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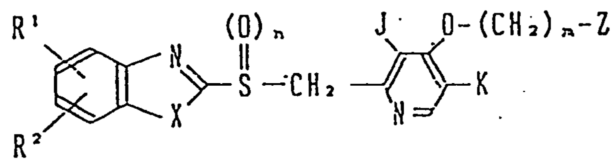
(54) **Pyridine derivatives, pharmaceutical compositions comprising the same, the use of the same for the manufacture of medicaments having therapeutic or preventative value, and process for preparing the same.**

(57) The invention provides pyridine derivatives represented by general formula:



wherein R^1 and R^2 may be the same or different from each other and each stand for a hydrogen atom, a C_{1-6} alkyl, C_{1-6} alkoxy, halogenated C_{1-6} alkyl, (C_{1-6} alkoxy)carbonyl or carboxyl group or a halogen atom;
X stands for a group represented by the formula:
-O-, -S- or

$$\begin{array}{c}-N-\\ |\\ R^3\end{array}$$

(wherein R^3 stands for a hydrogen atom or a C_{1-6} alkyl, phenyl, benzyl or (C_{1-6} alkoxy)carbonyl group);
Z stands for
① a group represented by the general formula:

$-O-(CH_2)_q-R^5$

wherein q stands for an integer of 1 to 3 and R^5 stands for a naphthyl group, which may be substituted with a C_{1-6} alkoxy group, a hydroxyl group or a halogen atom; a pyridyl group or a furyl group,
② a group represented by the general formula:

$-OR^9$

wherein OR^9 stands for a phenyl, tolyl, xylyl or naphthyl group,
n stands for an integer of 0 to 2; m stands for an integer of 2 to 10; and
J and K may be the same or different from each other and each stand for a hydrogen atom or a C_{1-6} alkyl group,
and a pharmaceutically acceptable salt thereof.

Pharmaceutical compositions comprising these derivatives are also provided, together with the use of the derivatives for the manufacture of medicaments having therapeutic or preventative value in the treatment of peptic ulcers. Processes for preparing such pyridine derivatives are also provided.

TECHNICAL FIELD

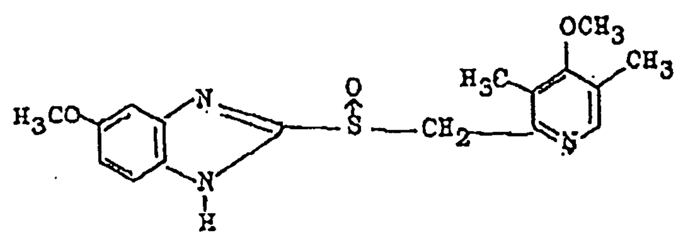
Novel pyridine derivatives exhibiting activity in treating or preventing peptic ulcers, pharmaceutical compositions containing them, and methods of medical treatment are described.

BACKGROUND ART

Duodenal and gastric ulcers, known collectively an peptic ulcers, are localized erosions of the mucous membrane of the duodenum or stomach, respectively, which expose the underlying layers of the gut wall to the acid secretions of the stomach and to the proteolytic enzyme pepsin. They are believed to be caused by autolysis which is caused by an imbalance between offensive factors, such as acid or pepsin, and defensive factors, such as resistance of the mucous membrane, mucilage secretion, bloodstream or control of the duodenum. Peptic ulceration is the most common disease of the gastro-intestinal tract and it is estimated that approximately 10 to 20% of the adult male population will experience at some time in their lives.

Peptic ulcers are cured or prevented by medical treatment, in principle, and many pharmacotherapies have been suggested, some with high degrees of success.

Clinically useful modialities include H_2-blockers, such as cimetidine and ranitidine, as anti-ulcer agents. It has been noted, more recently, that inhibitors of H^+-K^+-ATPase, an enzyme specifically present in the parietal cells of the stomach, can effectively inhibit the secretion of gastric acid in mammals, including man, therefore it has been expected that a new class of anti-ulcer agents from this viewpoint will come into existance. More specifically, a wide variety of compounds having a benzimidazole structure have been proposed. Among these compounds is Omeprazole, currently under active development, as the most promising compound; see U.S. Patent Nos. 4,337,257; 4,255,431; and 4,508,905. These patents describe compounds with a methoxy group in the 4-position of the pyridine ring. Omeprazole, having the formula:



and further 2-(4-methoxyethoxypyridine-2-yl)methylsulfinyl-5-methyl-1H-benzimidazole in the working examples thereof.

Related benzyimidazole-type compounds having anti-ulcer activities are described in published application GB 2,134,523A. More specifically, compounds in which the 4-position of the pyridine ring is substituted with an alkoxyalkoxy group with each alkoxy group containing 1-2 carbons are described. Example 157 of this patent describes 2-(3,5-dimethyl-4-methoxyethoxypyridine-2-yl)methylsulfinyl-5-phenyl-1H-benzimidazole. Other substitutions on various positions of the benzyl and pyridine rings are also described.

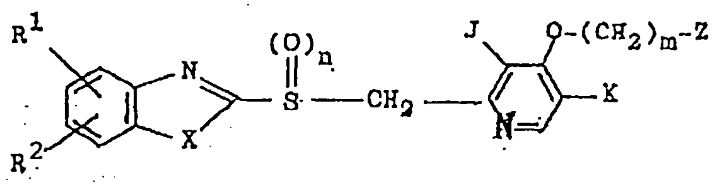
Biological tests reported in tables 4 and 5 of this published application report significant biological effects on gastric acid secretion, both in isolated cells and in laboratory animals, when the 4-position on the pyridine ring is substituted with a methoxy group.

Additional benzimidazole-type compounds, in which the substituent at the 4-position on the pyridine ring is a benzyloxy group, are described in European patent application 0,167,943.

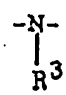
DISCLOSURE OF THE INVENTION

The present inventors have discovered a class of novel compounds with a more excellent anti-ulcer activity than Omeprazole which is regarded, at the present tine, as the most significant benzimidazole-type compound having anti-ulcer activity. As a result of intensive studies, it has been found that compounds represented by formula (I) are more potent in inhibiting gastric acid secretion in comparison with Omeprazole. The present invention has been accomplished on the basis of this finding.

The present invention includes a class of pyridine derivatives represented by the general formula:



where R^1 and R^2 may be the same or different, each being a hydrogen atom, a lower alkyl, lower alkoxy, halogenated lower alkyl, lower alkoxycarbonyl or carboxyl group or a halogen atom;
X is a group represented by the formula:
-o-, -s- or



(in which R^3 stands for a hydrogen atom or a lower alkyl, phenyl, benzyl or lower alkoxycarbonyl group); and
A represents:

1. a group of the formula:

$-O(CH_2)_p-O-R^4$

where p is an integer of 1 to 3 and R^4 is hydrogen atom or a lower alkyl, aryl or aralkyl group,

2. a group of the general formula:

$-O-(CH_2)_q-R^5$

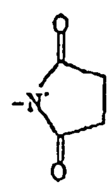
where q is an integer of 1 to 3 and R^5 is a halogen atom or an alkoxycarbonyl, aryl or heteroaryl group.

3. a group of the general formula:

$-O-(CH_2)_r-O-(CH_2)_s-O-R^6$

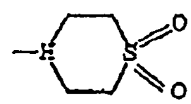
where r and s each independently are an integer of 1 to 5 and R^6 is a hydrogen atom or a lower alkyl group,

4. a group of the formula:

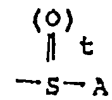


5. a group of the formula:

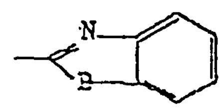
6. a group of the formula:



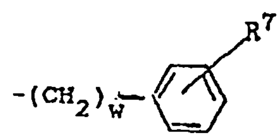
7. a group of the general formula:



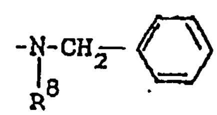
where t is an integer of 0 to 2 and A is a group of the general formula:



(where B is a group represented by the formula: -NH-, -O- or -S-), a lower alkyl, alkoxycarbonylmethyl, pyridyl or furyl group or a group of the general formula:



8. a group of the general formula:



where R^8 is an acetoxy or lower alkyl group,
or
9. a group of the general formula:

$-OR^9$

where R^9 is a hydrogen atom or a lower alkyl or aryl group;
n is an integer of 0 to 2; m is an integer of 2 to 10, and

J and K, which may be the same or different from each other, each stand for a hydrogen atom or a lower alkyl group, with the proviso that when Z is a group falling under the above category (9) R^9 is a lower alkyl group and m stands for an integer of 3 to 10,
and pharmaceutically acceptable salts thereof.

The same definitions for R^1, R^2, X, n, J, K, Z and m are used throughout the specification that follows and in the appended claims.

Also disclosed are pharmaceutical compositions containing those compounds as the active ingredient(s) and procedures for preventing or treating peptic ulcers in mammals, including humans, using these pharmaceutical compositions.

In the definition of the compounds of general formula (I) given above, the lower alkyl group defined above with respect to R^1, R^2, R^3, R^4, R^6, A, R^7, R^8, J and K in the compound (I) of the present invention

may be a straight-chain or branched alkyl groups having 1 to 6 carbon atoms. Examples include methyl, ethyl, n-propyl, n-butyl, isopropyl, isobutyl, 1-methylpropyl, tert-butyl, n-pentyl, 1-ethylpropyl, ixoamyl and n-hexyl groups, among which methyl and ethyl groups are most preferred.

The lower alkoxy group and the lower alkoxy moiety of the lower alkoxycarbonyl group defined above with respect to R^1 and R^2 may be an alkoxy group derived form the above lower alkyl group. Methoxy and ethoxy groups are most preferred.

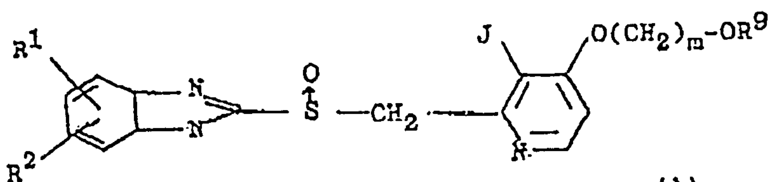
The halogen atom defined above includes chlorine, bromine, iodine or fluorine. The aryl group defined above with respect to R^4 and R^5 may be phenyl, tolyl, xylyl, naphthyl or the like which may be substituted with a lower alkoxy or hydroxyl group, a halogen atom or the like.

Examples of the arylalkyl defined above with respect to R^4 include benzyl and phenethyl groups.

Examples of the heteroaryl group defined above with respect to R^5 include pyridyl and furyl groups.

In the definition of Z in general formula (I), groups 1, 2, 3, 4, 5 and 9 are preferred; group 9 is the most preferred. As for R^1 and R^2, hydrogens for both and then a combination of a lower alkyl, inter alia methyl, for R^1 and hydrogen for R^2 are preferred. X is preferably $-NR^3$ where R^3 is hydrogen. A preferred value for n is 1. The preferred substituents for J and K are both hydrogen or where J is lower alkyl, inter alia methyl, and K is hydrogen, or when J is hydrogen K is lower alkyl, inter alia methyl. Thus, J or K are independently preferably hydrogen or methyl, most preferably J is methyl and K is hydrogen.

A first preferred class of compounds falling within the compounds of general formula (I) are represented by the following formula:



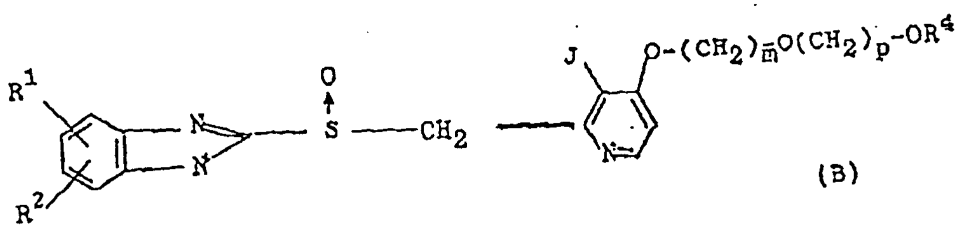
(A)

(where R^1, R^2, J, m and R^9 have the same meanings as defined above). In formula A, the preferred R^1 and R^2 substituents are both hydrogen, or R^1 is 5-lower alkoxy, 5-lower alkyl or 5-halogenated lower alkyl and R^2 is hydrogen. The preferred substituent for J is hydrogen or methyl; the preferred value for m is in the range of 3 to 10, the most preferred being 3; and the preferred R^9 substituent is lower alkyl, inter alia methyl, or aryl. Among these possibilities for the compounds of formula A the preferred combination is when R^1 and R^2 are both hydrogen, J is methyl, m is 3 and R^9 is methyl.

A second group of preferred compounds are combinations of the above substituents where both R^1 and R^2 are hydrogen, J is hydrogen, m is 3 and R^9 is methyl.

A third group of preferred compounds falling within formula A is when both R^1 and R^2 are hydrogen, J is methyl, m is 2 and R^9 is benzyl.

A second class of compounds falling within general formula (I) are represented by the following formula:



(B)

(where R^1, R^2, J, p, m and R^4 have the same meanings as given above). In formula (B), the preferred substituents for R^1 and R^2 are both hydrogen; or when R^1 is 5-lower alkoxy, 5-lower alkyl or 5-halogenated lower alkyl, R^2 is hydrogen. The preferred value of m is 2 or 3; the preferred value for p is 2 or 3; and the preferred substituent for R^4 is methyl or benzyl. Of the above possibilities for formula (B), the most preferred combination is where R^1 is 5-methyl, R^2 is hydrogen, J is methyl, m is 2, p is 2 and R^4 is methyl.

Examples of the pharmaceutically acceptable salt include salts with inorganic acids, such as hydrochloride, hydrobromide, sulfate and phosphate; those with organic acids, such as acatate, maleate, tartrate,

methanesulfonate, benzenesulfonate, and toluenesulfonate; and those with amino acids such as arginine, aspartic acid and glutamic acid.

Some of the compounds according to the present invention can form a salt with a metal such as Na, K, Ca or Mg. Those metal salts are also included among the pharmaceutically acceptable salts of the present invention. For example, compounds represented by the general formula (I), Wherein X is a group of

$$\begin{array}{c}-N-\\ |^{3}\\ R\end{array}$$

and R^3 is a hydrogen atom, or compounds represented by the general formula (I), wherein Z is a group falling under the category 7 and B is a group of -NH-, can be present as a metal salt,

Although the compounds of the present invention may also be present as a hydrate or as a stereoisomer, it is a matter of course that these hydrates and stereoisomers are also included in the scope of the present invention.

Now, the effect of the compounds of the present invention will be described by referring to the following pharmacological experiments.

Pharmacological Experiment

Inhibition against the activity of H^+-K^+ ATPase

(1) Preparation of H^+-K^+ ATPase

Prepared from the fundic glands of a fresh mucous membrane of a pig stomach according to a modified method of Saccomani et al. (see Biochem. and Biophys. Acta, 464, 313 (1977)).

(2) Measurement of the activity of H^+-K^+ ATPase

The compound of the present invention was incubated at various concentration in a 40 mM Tris-HCl buffer solution having a pH of 7.40 together with H^+-K^+ ATPase and 10 µg/ml of a protein at 37 °C for 30 minutes, followed by the addition of 15 mM KCl. After 10 minutes, the ATPase reaction was initiated by the addition of 3 mM of $MgCl_2$ and ATP. After 10 minutes, the amount of the released inorganic phosphoric acid was determined according to the method of Yoda and Hokin (see Biochem. Biophys. Res. Com., 40, 880 (1970)).

The test compound was used as a solution in methanol.

The inhibitory effect was determined by subtracting the amount of the released inorganic acid observed with respect to the case wherein a solution of a test compound was added from that with respect to the control wherein only a solvent was added to determine a difference and dividing this difference by the latter amount and shown by percentage. The inhibitory effect is shown in Table 1 in terms of IC_{50}.

(3) The results are shown in Table 1.

Table 1

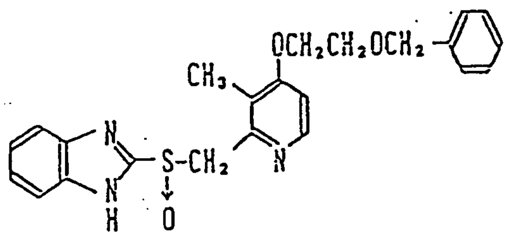
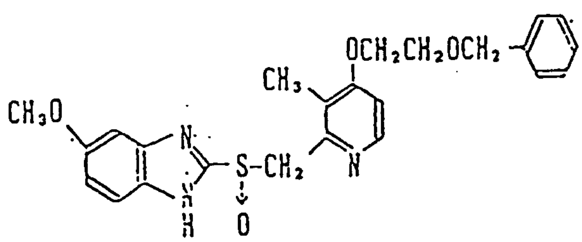
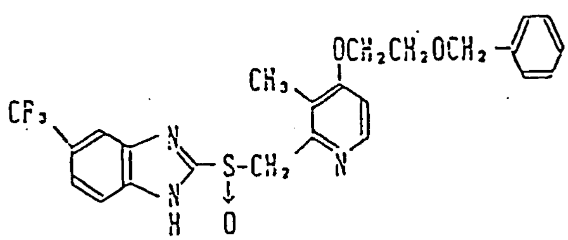
No.	Compound	IC_{50} (M)
1		9.2×10^{-7}
2		1.4×10^{-6}
3		1.0×10^{-6}

Table 1 (cont'd)

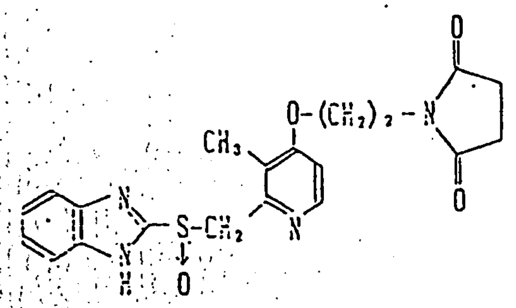
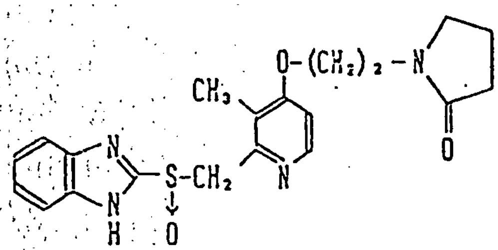
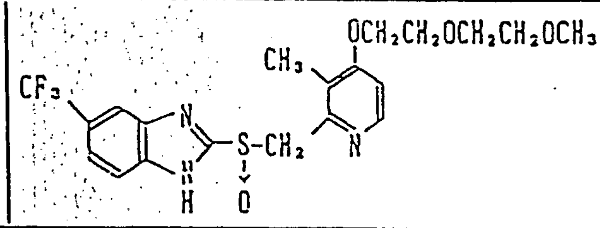
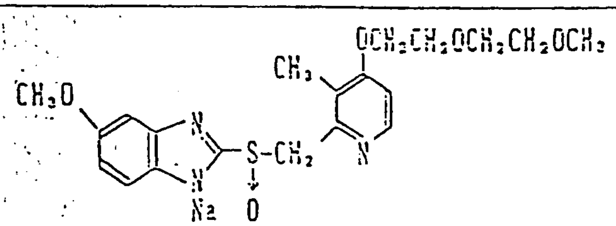
No.	Compound	IC_{50} (M)
4		1.1×10^{-6}
5		2.4×10^{-6}
6		5.5×10^{-7}
7		1.7×10^{-6}

Table 1 (cont'd)

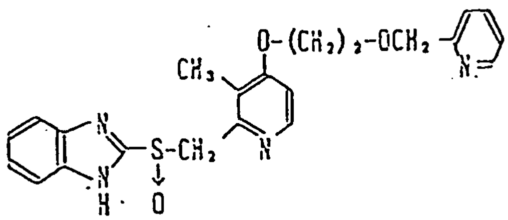
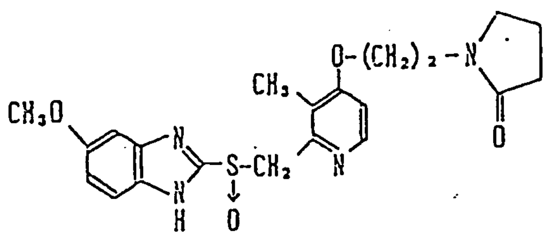
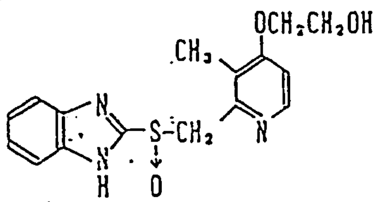
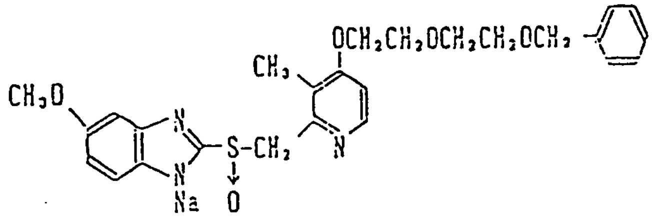
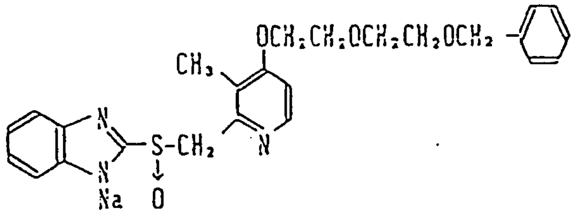
No.	Compound	IC_{50} (M)
8		1.2×10^{-6}
9		1.3×10^{-5}
10		1.9×10^{-6}
11		4.2×10^{-6}
12		2.6×10^{-6}

Table 1 (cont'd)

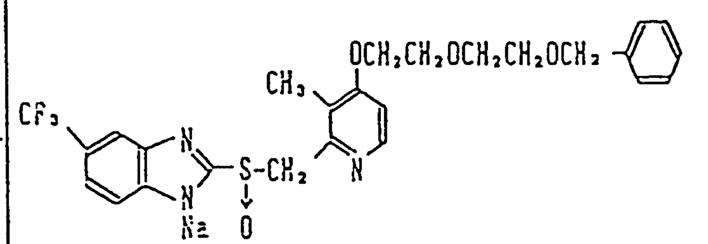
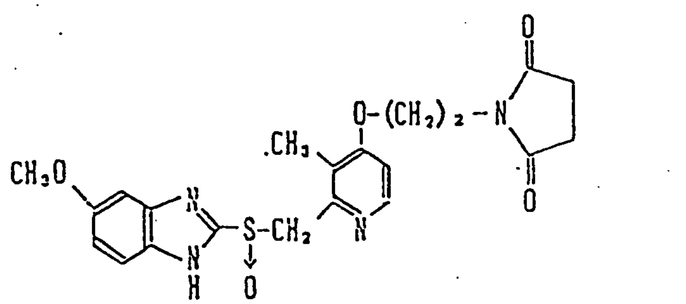
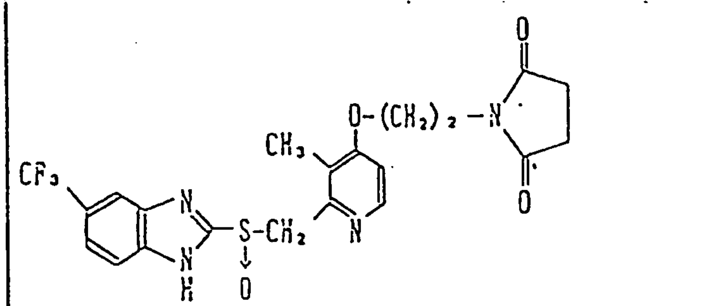
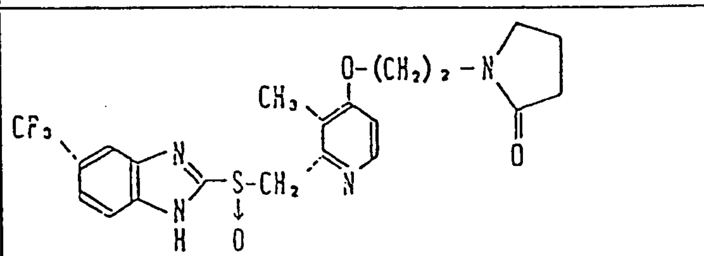
No.	Compound	IC_{50} (M)
13		6.3×10^{-7}
14		1.0×10^{-5}
15		7.2×10^{-6}
16		1.7×10^{-6}

Table 1 (cont'd)

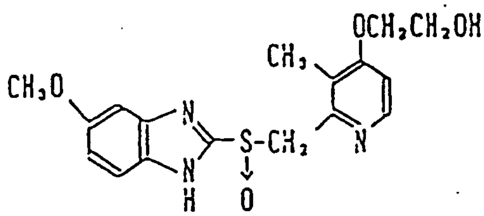
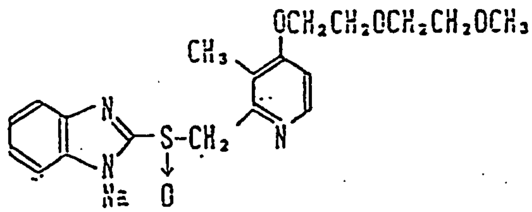
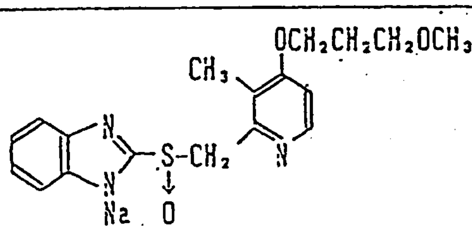
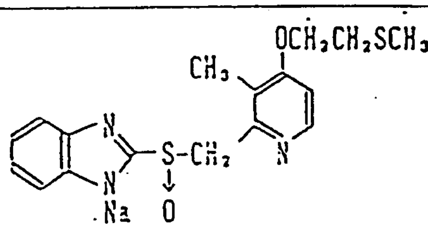
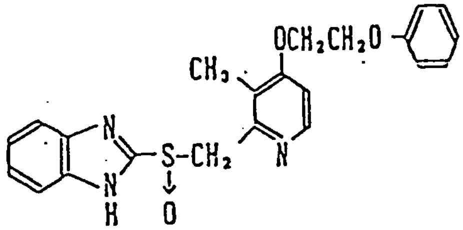
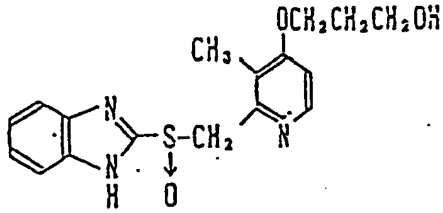
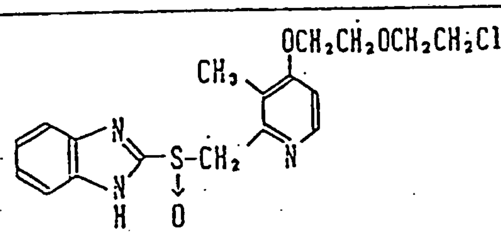
No.	Compound	IC_{50} (M)
17		3.5×10^{-6}
18		3.3×10^{-6}
19		1.7×10^{-6}
20		2.3×10^{-6}

Table 1 (cont'd)

No.	Compound	IC_{50} (M)
21		1.3×10^{-6}
22		1.9×10^{-6}
23		1.4×10^{-6}
24	Omeprazole	1.1×10^{-5}

It is apparent from the results of the experiments that the compound of the present invention exhibits a high inhibitory effect on the activity of H^+-K^+ ATPase and is highly safe, so that it can effectively inhibit the secretion of an acid and is therefore effective in the therapy or prevention of human and animal peptic ulcer.

Further, the compound of the present invention exhibits excellent recovery of the secretion of an acid and therefore is superior to the one of the prior art in this respect.

Chronic gastric fistula dogs were used. The test compound was intraduodenally administered to each dog in an amount of 4 mg per kg. In 1, 24, 48 and 72 hours, respectively, from the time of administration, pentagastrin (6 micron grams per kg) was injected intramuscularly into the dog. Gastric acid secretion, determined and recovery thereof, was determined in terms of percent of the control response. Results from this test are shown in Table 3.

From the results, it can be determined that within one hour from the intraduodenal administration the pentagastrin-stimulated gastric acid secretion was completely inhibited in both tests of compound 19 and Omaprazole. In the test, acid output with compound 19 was 61.9 percent and 121.5 percent in comparison with the control group after 24 and 48 hours, respectively. On the other hand, in the same test using Omeprazole, gastric acid secretion was 108.4 percent after 72 hours. With both compound 19 and

Omeprazole, 48 hours and 72 hours were required for the acid secretion to recover, respectively.

Pharmacological Experiment 2 -

Inhibitory effect on gastric acid secretion

Chronic gastric fistula dogs were used. Gastric acid secretion of each dog was stimulated by infusing 100 micron grams per kg per hour of histamine. After one hour of histamine infusion, each of the test compounds was administered intraduodenally to each dog, and after one hour of administration, the amount of gastric acid secretion of each test dog was determined. Results were compared with the control group to which no test compound had been administered and are expressed in terms of percent inhibition.

The inhibitory effect exhibited by the test compound on the histamine-stimulated gastric acid secretion of the chronic gastric fistula dogs is shown in Table 2. The values of ID 50, calculated from the dose-inhibition curve of the test compounds, are 59.9 micron grams per kg for compound 19 and 112.2 micron grams per kg for Omeprazole, demonstrating that compound 19 was two times more potent than Omeprazole. Compound 19 is shown in Table 1 of Experiment 1 and in working example 33 shown below.

Table 2

μg/Kg	% Inhibition of acid output	
	compound 19	omeprazole
31.25	34.4	-
62.5	50.1	41.1
125	67.7	48.6
250	87.4	62.1
500	100.0	91.2
1000		100.0

Table 3

Compound	1 hr	24 hr	48 hr	72 hr
compound 19	0	61.9	-	-
Omeprazole	0.3	32.3	69.1	108.4

The results of the three pharmacological experiments as reported above demonstrate that the compound of the invention exhibits a significant inhibitory effect on the activity of H^+-K^+ATPase.

Among these compounds, compound 19 of the invention unexpectedly has a more potent inhibitory activity on gastric acid secretion as compared with Omeprazole, which itself is highly inhibitory of gastric acid secretion among the compounds having a benzimidazole-type structure.

Further, it should be noted that the compound of the present invention unexpectedly exhibits a faster recovery or resumption of gastric acid secretion than Omeprazole.

At present, this H^+-K^+ATPase-inhibiting agent is believed to have a more potent inhibitory activity against gastric acid secretion than an H_2-blocker compound, and thus, in the future, may be the drug of

choice for the treatment of ulcers.

But, while more potent inhibitory activity against gastric acid secretion is desirable, too long-lasting inhibition of gastric acid secretion is not preferable for an anti-ulcer agent. For example, it gives rise to the proliferation of Enterochromaffin-like cells (ECL cell) and formation of carcinoid derived from hypergastrinemia; see "Digestion", vol. 35, suppl. 1, page 42 to 55 (1986); the increase in the gastric bacterial flora and endogenous production of N-nitro compounds; see "Brit. Med. J.", vol. 289, page 717 (1984); and difficulty in determining the appropriate dosage regimen.

Thus, an H^+-K^+ATPase-inhibitory agent which possesses an excellent recovery of gastric acid secretion is most preferred.

No toxicological influence has been observed for compound 19 (working example 33), which is a representative compound of this invention, in beagle dogs to which it was orally administered at 10 mg/kg per day for one week, and in rats to which it was orally administered at 50 mg/kg per day for one week.

Thus, compound 19, as representative of this invention, exhibits a significant inhibitory effect upon the activity of H^+-K^+ATPase coupled with the desirable property of excellent gastric acid secretion recovery.

Compound 19, as representative of the compounds of this invention, is thus considered to be effective in the treatment or prevention of peptic ulcers (stomach ulcers and duodenal ulcers) in animals, including humans.

The compounds of the present invention are administered for the therapy or prevention of peptic ulcers either orally as powders, granules, capsules or syrup, or parenterally as an injection, or as an external preparation or drop, or as a suppository. Although the dose remarkably varies depending upon symptoms, age or kind of ulcer(s), it may be about 0.01 to 200 mg/kg, preferably 0.05 to 50 mg/kg, still preferably 0.1 to 10 mg/kg a day, and may be administered in a single dose or in divided doses, for example from 2 to 4 times a day.

The drug may be formulated into pharamceutical presentations using conventional formulation procedures. More specifically, a solid drug for oral application can be prepared by mixing an active principle with filler and, if necessary, binder, disintegrating agent, lubricant, coloring agent, corrigent or the like and converting the obtained mixture into a tablet, coated tablet, granule, powder or capsule.

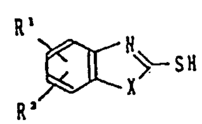
Examples of the filler include lactose, corn starch, sucrose, glucose, sorbitol, crystalline cellulose and silicon dioxide, while those of the binder include polyvinyl alcohol, polyvinyl ether, ethylcellulose, methylcellulose, acacia, tragacanth, gelatin, shellac, hydroxypropylcellulose, hydroxypropylstarch and polyvinylpyrrolidone. Examples of the disintegrating agent include starch, agar, gelatin powder, crystalline cellulose, calcium carbonate, sodium hydrogencarbonate, calcium citrate, dextrin and pectin, while those of the lubricant include magnesium stearate, talc, polyethylene glycol, silica and hardened vegatable oils. The coloring agent may be any one which is permitted to be added to drugs. Examples of the corrigent include cacao powder, mentha herb, aromatic powder, mentha oil, borneol and powdered cinnamon bark. Of course, these tablets and granules may be, if necessary, coated with sugar, gelatin or the like.

The injection can be prepared by mixing an active principle with pH adjusting agent, buffer, stabilizer, solubilizing agent or the like and treating the obtained mixture according to an ordinary process to obtain a subcutaneous, intramuscular or intravenous injection.

Preparation process

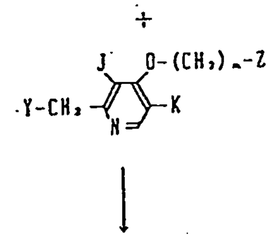
The compound of the present invention can be prepared by various processes, representative examples of which will now be described.

Preparation process A



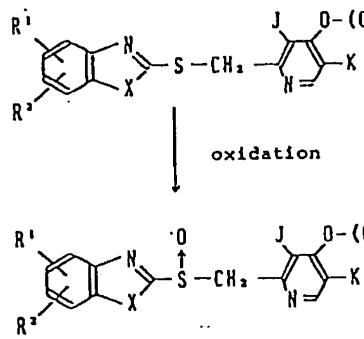
(II)

wherein R^1, R^2 and X are as defined above



(III)

wherein m, Z, J and K are as defined above and Y stands for a halogen atom or a sulfonyloxy group



(I')

(I")

That is, a compound represented by the general formula (II) is reacted with a halide or sulfonate represented by the general formula (III) to obtain a compound represented by the general formula (I') which is an objective compound of the present invention.

Examples of the halogen atom defined with respect to Y include chlorine, bromine and iodine, while those of the sulfonyloxy group include alkylsulfonyloxy groups such as methylsulfonyloxy and ethylsulfonyloxy groups and aromatic sulfonyloxy groups such as benzenesulfonyloxy and tosyloxy groups.

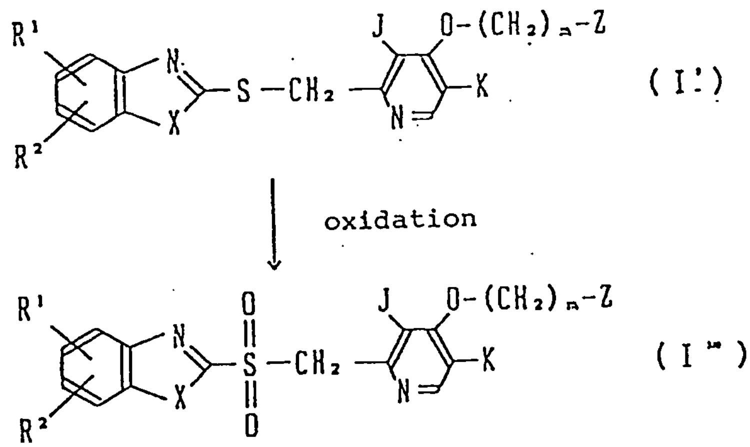
The above reaction is preferably carried out in the presence of an acid scavenger. Examples of the acid scavenger include carbonates and hydrocarbonates of alkali metals, such as potassium carbonate, sodium carbonate and sodium hydrogencarbonate; alkali hydroxides such as sodium hydroxide and potassium hydroxide and organic amines such as pyridine and triethylamine. Examples of the solvent to be used in the reaction include alcohols such as methyl and ethyl alcohols, tetrahydrofuran, dioxane, dimethylformamide, dimethyl sulfoxide and mixtures thereof with water.

The reaction temperature may be from -40 °C to the boiling point of the solvent used, preferably from about 0 to 60 °C.

The obtained compound (I') can be easily oxidized into its sulfinyl derivative (I") which is an objective compound of the present invention corresponding to a compound of the general formula (I) wherein n is 1.

This oxidation can be carried out according to an ordinary process by the use of an oxidizing agent such as hydrogen peroxide, peracetic acid, m-chloroperbenzoic acid, sodium hypochlorite or sodium hypobromite. The solvent to be used in the oxidation is generally selected from among dichloromethane, chloroform, benzene, toluene, methanol, ethanol and the like. The oxidation temperature may be from -70 °C to the boiling point of the solvent used, preferable from -60 to 25 °C.

Furthermore, a sulfone derivative which is an objective compound of the present invention corresponding to a compound of the formula (I) wherein n is 2 can be prepared by, for example, the following process:



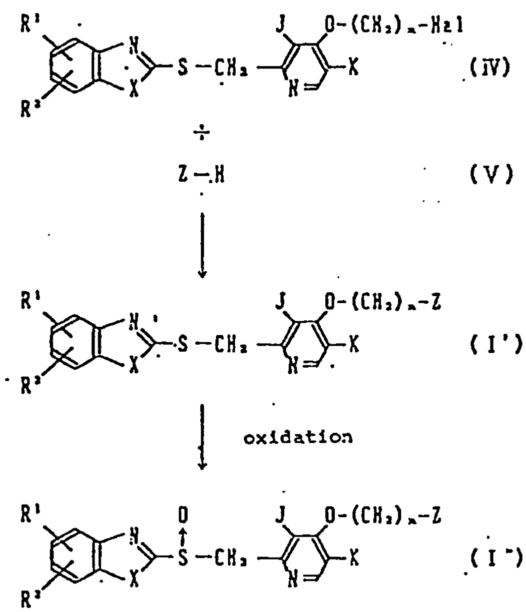
wherein R^1, R^2, X, J, m and Z are as defined above.

That is, the thio ether derivative represented by the general formula (I') which is an objective compound of the present invention is oxidized into its sulfone derivative represented by the general formula (I''') which is another objective compound of the present invention.

More precisely, the sulfone derivative (I''') which is an objective compound of the present invention can be prepared by dissolving the compound (I') in a solvent selected from among aromatic hydrocarbons such as benzene, toluene and xylene; halogenated hydrocarbons such as dichloromethane, chloroform and carbon tetrachloride; water; alcohols such as methanol and ethanol; ethyl acetate; acetone; acetic acid and the like to obtain a solution, adding at least twice by equivalent as much oxidizing agent selected from among hydrogen peroxide, peracetic acid, m-chloroperbenzoic acid, sodium hypochlorite, sodium m-periodate and the like to the solution under cooling with ice or at a room temperature and reacting the compound (I') with the oxidizing agent.

Alternatively, the sulfone derivative (I''') can be prepared by dissolving the sulfoxide derivative (I'') obtained by the above process in a solvent such as chloroform, adding an oxidizing agent such as m-chloroperbenzoic acid to the obtained solution and reacting the sulfoxide derivative (I'') with the oxidizing agent.

Preparation process B



wherein R^1, R^2, X, m, J, K and Z are as defined above and Hal stands for a halogen atom.

That is, an objective compound represented by the general formula (I) can be prepared by reacting a halide represented by the general formula (IV) with an alcohol, thiol or amine represented by the general formula: Z-H (V). This reaction is preferably carried out in the presence of an acid scavenger. Examples of the acid scavenger include carbonates and hydrogencarbonates of alkali metals, such as potassium carbonate and sodium carbonate; alkali hydroxides such as sodium hydroxide and potassium hydroxide and triethylamine. Examples of the solvent to be used in the reaction include ethers such as tetrahydrofuran and dioxane; ketones such as acetone and methyl ethyl ketone; benzene homologues such as benzene, toluene and xylene; acetonitrile; dimethylformamide; dimethyl sulfoxide and hexamethylphosphoric triamide. The reaction may be carried out either under cooling with ice or at a temperature not exceeding the boiling point of the solvent used.

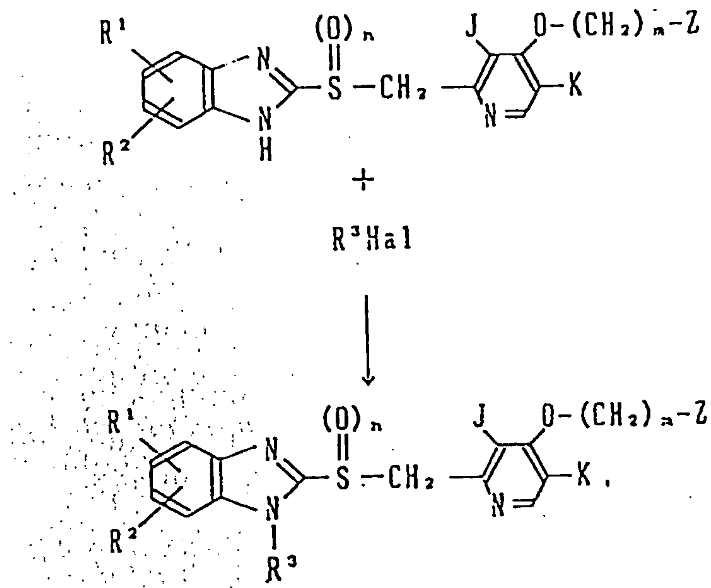
The obtained compound (I') which is an objective compound of the present invention can be oxidized into its sulfinyl derivative represented by the general formula (I") in a similar manner to that described above in Preparation process A.

Preparation process C

A compound represented by the general formula (I) wherein X is a group represented by the formula:

$$\begin{array}{c}-N-\\ |\\ R^3\end{array}$$

(wherein R^3 is a group selected from among those defined above except a hydrogen atom) can be prepared by the following process:



(VI)

(VII)

(I"")

wherein R^1, R^2, n, J, K, m and Z are as defined above; Hal stands for a halogen atom and R^3 is a group selected from among those defined with respect to R^3 of the formula (I) except a hydrogen atom, i.e., a lower alkyl, phenyl, benzyl or lower alkoxycarbonyl group.

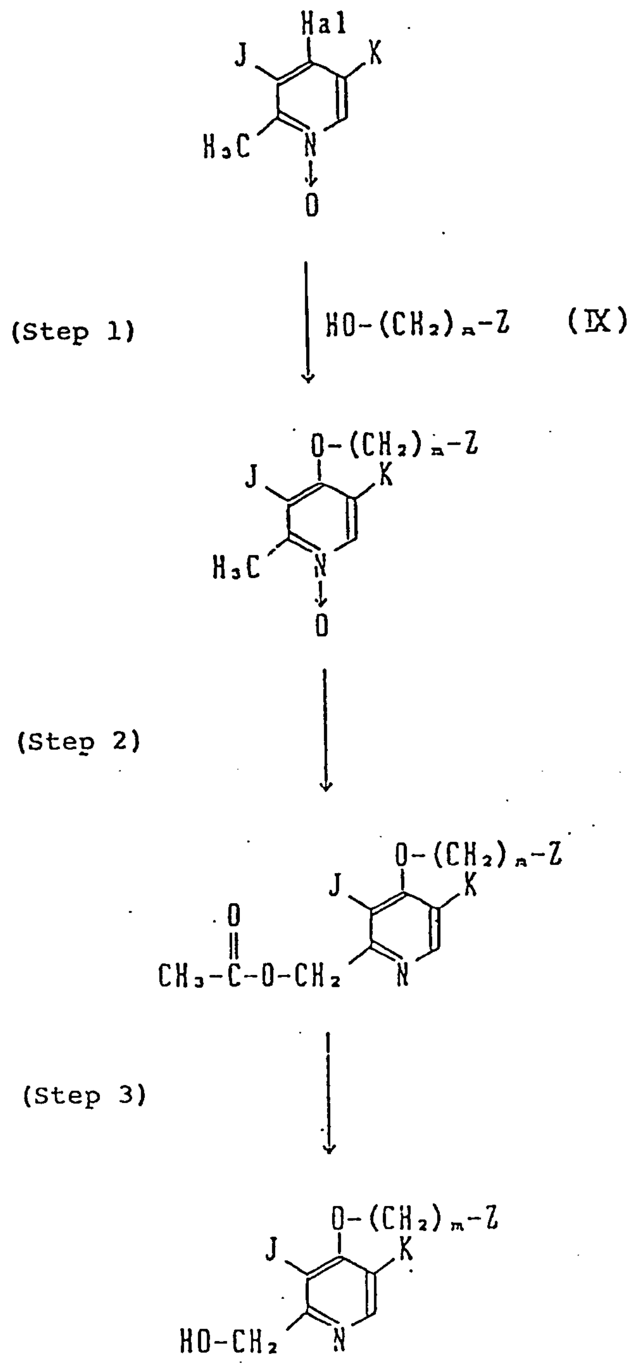
That is, a compound represented by the general formula (I"") which is an objective compound of the present invention can be prepared by condensing a compound represented by the general formula (VI) with a halide represented by the general formula (VII) according to an ordinary process.

This condensation is carried out in the absence of any solvent or in an organic solvent inert to the condensation selected from among benzene, ethanol, xylene, tetrahydrofuran, chloroform, carbon tetrachloride, dimethylformamide and the like either at a room temperature or under cooling with ice or heating for several hours according to an ordinary process. The condensation can be expedited by the use of a dehydrohalogenating agent selected from among inorganic salts such as sodium hydrogencarbonate, potassium carbonate, sodium carbonate and caustic soda or organic bases such as triethylamine, pyridine, pyrimidine and diethylaniline.

Further, the thio ether derivative represented by the general formula (I""), wherein n is 0, which has been prepared by condensing a compound represented by the general formula (VI), wherein n is 0, with a halide (VII) can be easily oxidized into the corresponding sulfoxide (n = 1) or sulfone (n = 2)derivative according to the same process as that described above.

Process for the preparation of starting materials

The compound represented by the general formula (III) to be used in the Preparation process A as a starting material can be prepared by, for example, the following process:


Hal
J
K
H_3C
N
O
(Step 1)
$HO-(CH_2)_m-Z$
(IX)
$O-(CH_2)_m-Z$
(Step 2)
(Step 3)
$CH_3-C(=O)-O-CH_2$
$HO-CH_2$

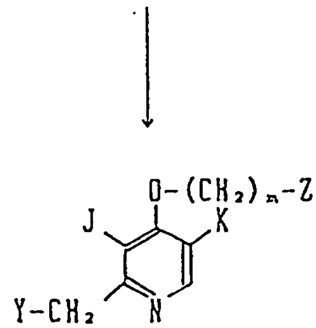
(VIII)

(X)

(XI)

(XII)

(Step 4)



(III)

wherein m, Z, J, K and Y are as defined above.

(Step 1)

A 4-halogenopyridine oxide derivative (VIII) (for example, 4-chloro-2,3-dimethylpyridine 1-oxide) is reacted with an alcohol derivative represented by the general formula (IX) in the presence of a base to obtain an alkoxy derivative represented by the general formula (X).

Examples of the base include alkali metal hydrides such as sodium hydride and potassium hydride; alkali metals such as metallic sodium; sodium alcoholates such as sodium methoxide and alkali metal hydroxides such as sodium hydroxide and potassium hydroxide. This reaction is carried out either in the absence of any solvent or in a solvent selected from among ethers such as tetrahydrofuran and dioxane; ketones such as acetone and methyl ethyl ketone; benzene homologues such as benzene, toluene and xylene; acetonitrile; dimethylformamide; dimethyl sulfoxide; hexamethylphosphoric triamide and the like at a temperature of from one under cooling with ice to the boiling point of the solvent used.

(Step 2)

The alkoxy derivative of the general formula (X) prepared in the Step 1 is heated in acetic anhydride to a temperature of about 60 to 100°C to obtain an acetoxymethylpyridine derivative represented by the general formula (XI).

(Step 3)

The acetoxymethylpyridine derivative (XI) prepared in the Step 2 is hydrolyzed into the corresponding 2-hydroxymethylpyridine derivative represetned by the general formula (XII).

This hydrolysis is generally carried out under alkaline conditions.

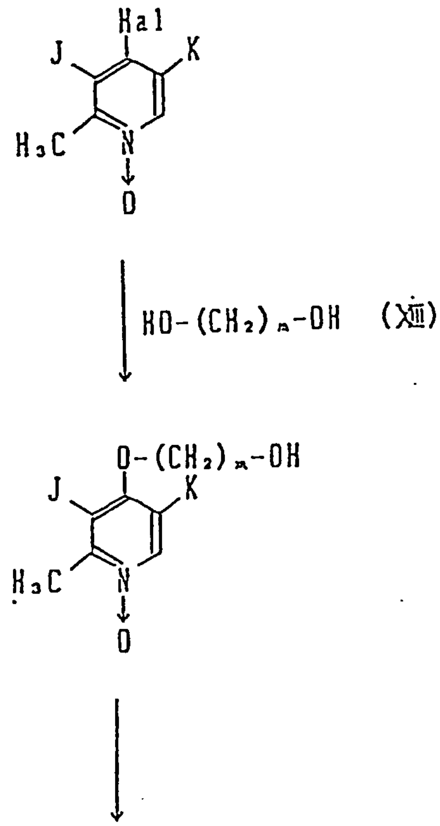
(Step 4)

The 2-hydroxymethylpyridine derivative (XII) prepared in the Step 3 is halogenated with, for example, a chlorinating agent such as thionyl chloride into a 2-halogenomethylpyridine derivative represented by the general formula (III). In this halogenation, for example, chloroform or dichloromethane is used as a solvent. Further, the 2-hydroxymethylpyridine derivative (XII) is reacted with an active sulfonyl chloride such as methanesulfonyl chloride to obtain a sulfonyloxy derivative represented by the general formula (III). In this reaction, for example, chloroform, dichloromethane, ether, tetrahydrofuran, pyridine or benzene is used as a solvent.

Alternatively, the compound represented by the general formula (X) to be used in the above process can be prepared by the following process:

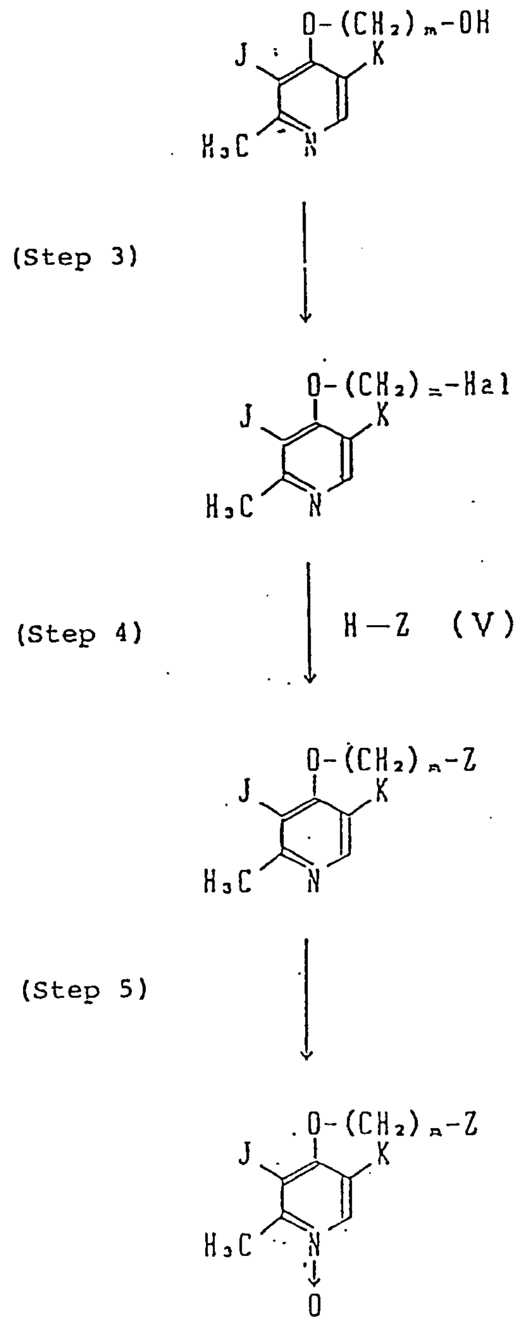
(VIII)

(Step 1)



(XIV)

(Step 2)



(XV)

(XVI)

(XVII)

(X)

(Step 1)

A compound represented by the general formula (VIII), wherein Hal stands for a halogen atom such as chlorine atom, is condensed with a compound represented by the general formula (XIII) according to an ordinary process to obtain a compound represented by the general formula (XIV).

This condensation is preferably carried out in the presence of a base selected from among alkali metal hydrides such as sodium hydride and potassium hydride; alkali metals such as metallic sodium; alkali metal hydroxides such as sodium hydroxide and potassium hydroxide and the like.

The condensation is carried out either in the absence of any solvent or in a solvent selected from among ethers such as tetrahydrofuran and dioxane; ketones such as acetone and methyl ethyl ketone; benzene homologues such as benzene, toluene and xylene; acetonitrile; dimethylformamide; dimethyl sulfoxide; hexamethylphosphoric triamide and the like at a temperature suitably selected from the range of one under cooling with ice to the boiling point of the solvent used.

(Step 2)

The obtained alkoxy derivative (XIV) is reduced into the compound (XV). Precisely, the alkoxy derivative (XIV) is hydrogenated in the presence of a 10% palladium/carbon catalyst in an acetic anhydride/acetic acid mixture to obtain the reduction product (XV).

(Step 3)

The obtained compound (XV) is halogenated with, for example, a chlorinating agent such as thionyl chloride to obtain a 2-halogenoethyl derivative represented by the general formula (XVI). In this halogenation, for example, chloroform or dichloromethane is used as a solvent.

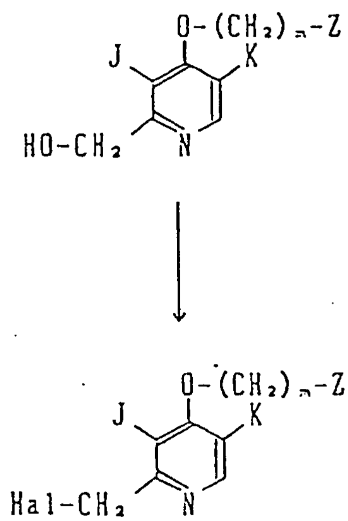
(Step 4)

The obtained compound (XVI) is reacted with an alcohol, thiol or amine represented by the general formula (V) to obtain a compound represented by the general formula (XVII). This reaction is preferably carried out in the presence of an acid scavenger as in the reaction of the Preparation process B.

(Step 5)

The obtained compound (XVII) is oxidized with an oxidizing agent such as hydrogen peroxide, peracetic acid or m-chloroperbenzoic acid to obtain the corresponding N-oxide derivative.

Alternatively, the compound represented by the general formula (III) to be used in the Preparation process A as a starting material can be prepared by the following process:



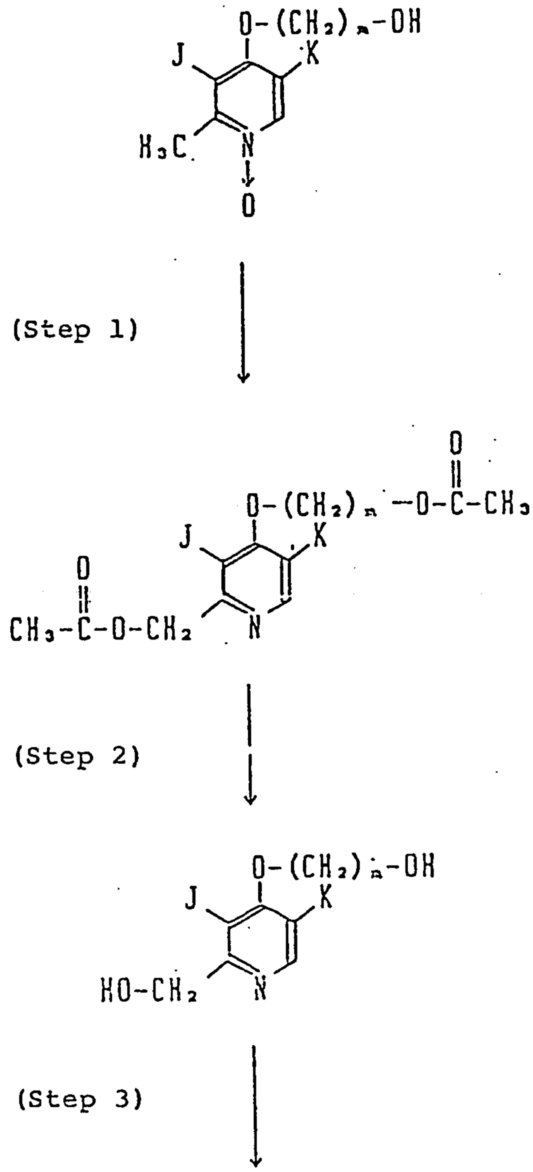
(XII)

(III)

wherein Hal stands for a halogen atom and Z and m are as defined above.

A compound represented by the general formula (XII) is halogenated with, for example, a chlorinating agent such as thionyl chloride at a temperature of 0 °C to a room temperature to obtain a halogenomethylpyridine derivative represented by the general formula (III). In this halogenation, for example, chloroform or dichloromethane is used as a solvent.

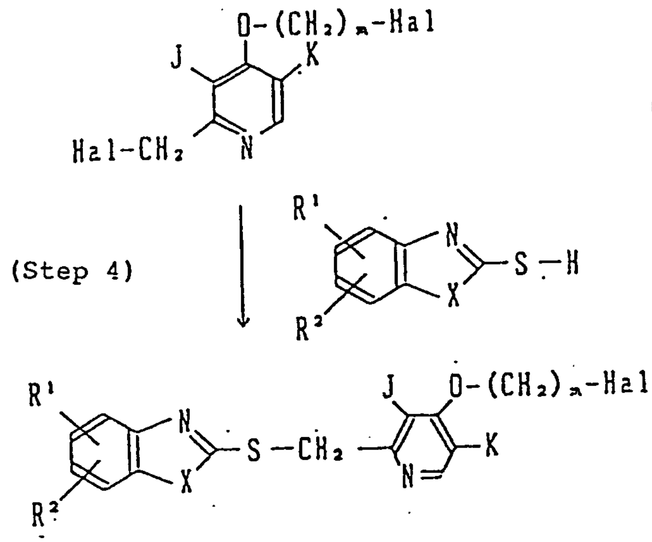
The compound (IV) to be used in the Preparation process B as a starting material can be prepared by, for example, the following process:



(XII)

(XIII)

(XIV)



(XX)

(Step 4)

(II)

(IV)

wherein Hal stands for a halogen atom and the others are as defined above.

(Step 1)

A compound represented by the general formula (XIV) is converted into the corresponding acetylate (XVIII) according to an ordinary process. For example, acetic anhydride or acetyl chloride is used in this reaction.

(Step 2)

The obtained acetylate is hydrolyzed in the pressence of an acid or a base to obtain the corresponding diol derivative (XIX).

(Step 3)

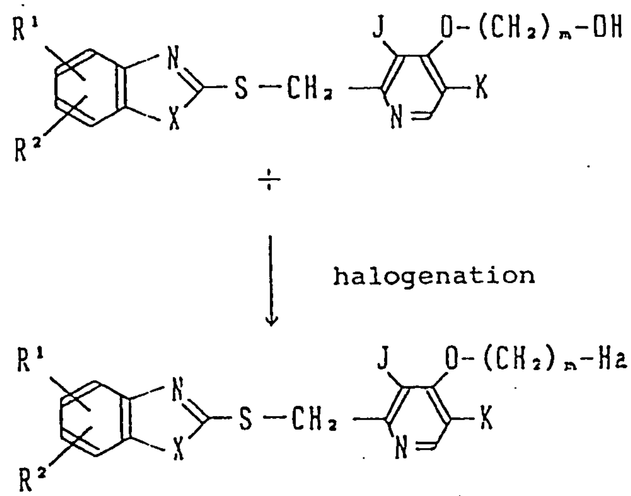
The diol derivative (XIX) is halogenated with, for example, a chlorinating agent such as thionyl chloride to obtain a dihalide represented by the general formula (XX). In this halogenation, for example, chloroform or dichloromethane is used as a solvent.

(Step 4)

The obtained dihalide (XX) is reacted with a compound represented by the general formula (II) to obtain a sulfide derivative represented by the general formula (IV).

This reaction is carried out in the presence of an acid scavenger selected from among carbonates and hydrogencarbonates of alkali metals, such as potassium carbonate and sodium carbonate, and alkali hydroxides such as sodium hydroxide and potassium hydroxide. Examples of the solvent to be used in the reaction include alcohols such as ethanol and methanol, tetrahydrofuran, dioxane, dimethylformamide, dimethyl sulfoxide and mixtures thereof with water. The reaction temperature may be from 0 °C to the boiling point of the solvent used, preferably from about 40 to 60 °C.

Alternatively, the compound (IV) to be used in the Preparation process B as a starting material can be prepared by the following process:



(I''''')

(IV)

wherein Hal stands for a halogen atom and the others are as defined above.

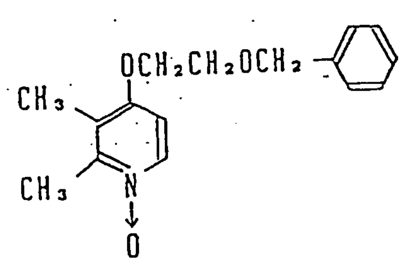
That is, the compound (IV) can be obtained by halogenating the compound (I''''') which is an objective compound of the present invention and prepared by the Preparation process A according to an ordinary process. More precisely, a compound represented by the general formula (I''''') is halogenated with, for example, a chlorinating agent such as thionyl chloride to obtain a halide represented by the general formula (IV). In this halogenation, chloroform or dichloromethane is preferably used as a solvent and the reaction temperature ranges preferably from a room temperature to about 80 °C.

Examples of the present invention will now be described, though it is needless to say that the present invention is not limited by them at all.

The following Preparative Examples refer to the preparation of raw materials to be used in the preparation of the objective compounds according to the present invention.

Preparative Example 1

Synthesis of 4-(2-benzyloxyethoxy)-2,3-dimethylpyridine N-oxide

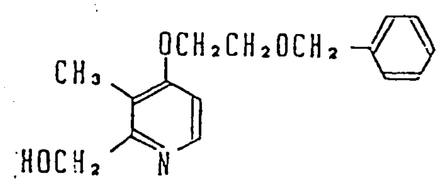


1.82 g (79.13 mmol) of Na was added to 50 ml of benzyloxyethanol to obtain a mixture. This mixture was stirred at 50 °C for 2 hours. 5.0 g (31.76 mmol) of 4-chloro-2,3-dimethylpyridine N-oxide was added to the resulting mixture at a room temperature. The obtained mixture was stirred at 110 °C for 1.5 hours, cooled to a room temperature and filtered to remove insoluble matter. The filtrate was adsorbed to silica gel with dichloromethane. The silica gel was treated with 5 to 30% ethyl acetate in hexane to elute benzyloxyethanol. Then, the resulting silica gel was treated with 5 to 30% methanol in ethyl acetate to obtain 7.15 g of 4-(2-benzyloxyethoxy)-2,3-dimethylpyridine N-oxide as an oil.

^{1}H-NMR($CDCl_3$) δ ; 2.20(s,3H), 2.47(s,3H), 3.8 ~4.0(m,2H), 4.1~4.25(m,2H), 4.6 (s,2H), 6.65(d,J = 7.03Hz,1H), 7.33(s,5H), 8.12(d,J = 7.03Hz,1H)

Preparative Example 2

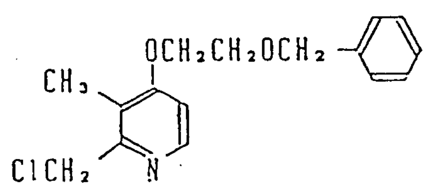
Synthesis of 4-(2-benzyloxyethoxy)-2-hydroxymethyl-3-methylpyridine



A mixture comprising 6.5 g of 4-(2-benzyloxyethoxy-2,3-dimethylpyridineN-oxide and 56 ml of acetic anhydride was stirred at 80 to 90 °C for one hour and distilled to remove the acetic anhydride. The obtained residue was made weakly basic with an aqueous solution of sodium carbonate and extracted with methyl ethyl ketone. The extract was dried over magnesium sulfate and distilled to remove the methyl ethyl ketone. Thus, 7.0 g of 2-acetoxymethyl-4-(2-benzyloxyethoxy)-3-methylpyridine was obtained. This intermediate was dissolved in 90 ml of ethanol, followed by the addition of 1.43 g of sodium hydroxide. The obtained mixture was stirred at 40 °C for one hour, followed by the addition of water. The mixture was extracted with methyl ethyl ketone. The obtained extract was dried over magnesium sulfate to obtain 5.4 g of 4-(2-benzyloxyethoxy)-2-hydroxymethyl-3-methylpyridine.
^{1}H-NMR($CDCl_3$) δ ;2.06(s,3H), 3.7 ~3.95(m, 2H), 4.0~4.3(m,2H), 4.6(s,4H), 6.70(d, J=6.7Hz,1H), 7.33 (s,5H), 8.27(d,J=6.7 Hz,1H)

Preparative Example 3

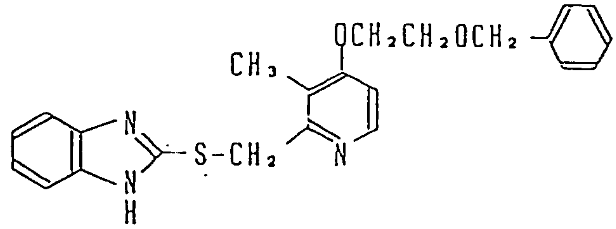
Synthesis of 4-(2-benzyloxyethoxy)-2-chloromethyl-3-methylpyridine



5.3 g of 4-(2-benzyloxyethoxy)-2-hydroxymethyl-3-methylpyridine was dissolved in 60 ml of chloroform to obtain a solution. A solution of 5.8 g of thionyl chloride in 40 ml of chloroform was dropwise added to the above solution under cooling with ice. The obtained mixture was stirred at a room temperature for 7 hours and distilled under a reduced pressure to obtain a residue. 200 ml of a 2N aqueous solution of sodium carbonate was added to the residue. The obtained mixture was extracted with chloroform and the extract was dried over magnesium sulfate and distilled to remove the chloroform. 6.3 g of the title compound was obtained.
^{1}H-NMR($CDCl_3$) δ ;2.27(s,3H), 3.5~4.25(m, 4H), 4.56(s,2H), 4.66(s,2H), 6.7(d,J= 5.71Hz,1H), 7.30(s,5H), 8.27(d,J=5 71Hz, 1H)

Example 1

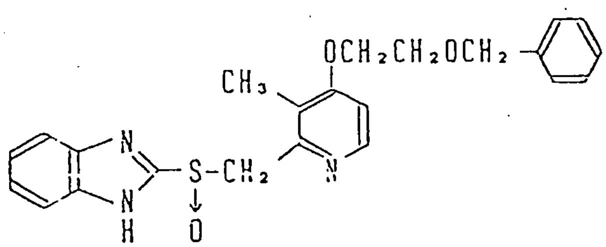
2-[{4-(2-Benzyloxyethoxy)-3-methylpyridine-2-yl}methylthio]benzimidazole



A mixture comprising 1.0 g of 2-mercaptobenzimidazole, 2.0 g of 4-(2-benzyloxyethoxy)-2-chloromethyl-3-methylpyridine, 302 mg of sodium hydroxide and 40 ml of ethanol was stirred under heating at 60 °C for 1.5 hours and distilled under a reduced pressure to remove the ethanol. The obtained residue was subjected to silica gel column chromatography. The column was treated with 30 to 60% ethyl acetate in n-hexane to obtain 2.0 g of the title compound as a white crystal.
^{1}H-NMR($CDCl_3$) δ ; 2.28(s,3H), 3.8 ~3.9(m, 2H), 4.15 ~4.25(m,2H), 4.37(s,2H), 4.62 (s,2H), 6.74-(d,J=5.71Hz,1H), 7.11 ~7.65 (m,9H), 8.32(d,J=5.71Hz,1H)

Example 2

2-[{4-(2-Benzyloxyethoxy)-3-methylpyridine-2-yl}methylsulfinyl]benzimidazole



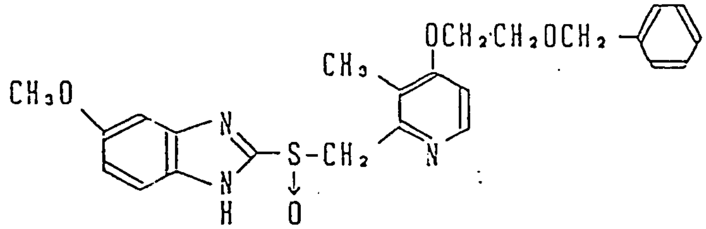
0.98 g of the thio ether prepared above was dissolved in 40 ml of dichloromethane to obtain a solution. 521 mg of m-chloroperbenzoic acid was added to the solution in portions at a temperature of -30 to -40 °C, followed by the addition of 461 mg of triethylamine. The obtained mixture was heated to 0 °C, followed by the addition of 20 ml of a 1N aqueous solution of sodium carbonate. The obtained mixture was stirred for 30 minutes and extracted with dichloromethane. The extract was washed with a saturated aqueous solution of common salt, dried over magnesium sulfate and distilled to remove the dichloromethane. The obtained residue was crystallized from a dichloromethane/ether mixture to obtain 0.78 g of the title compound as a crystal.
M^{+1} (determined according to FAB mass spectrometry: the same applies hereinafter): 422
^{1}H-NMR($CDCl_3$) δ ; 2.2(s,3H), 3.65~3.98(m, 2H), 4.04 ~4.28(m,2H), 4.59(s,2H), 4.78(s,2H), 6.98-(d,J=4.6Hz,1H), 7.05~ 7.8(m,9H), 8.22(d,J=4.6Hz,1H), 13.6(bs, 1H)

Examples 3 to 5

The following compounds were prepared in a similar manner to that described in Example 1 or 2.

(Example 3)

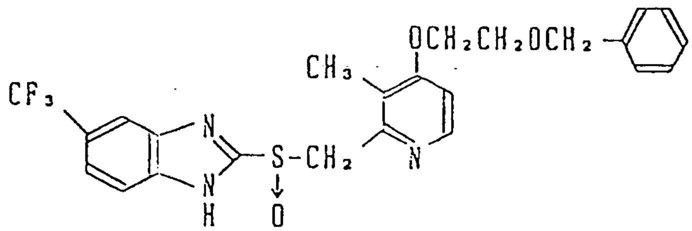
2-[{4-(2-Benzyloxyethoxy)-3-methylpyridine-2-yl}methylsulfinyl]-5-methoxy-1H-benzimidazole



^{1}H-NMR($CDCl_3$) δ ;2.13(s,3H), 3.78(s,3H), 3.62~3.90(m,2H), 4.1~4.3(m,2H), 4.5 (s,2H), 4.7(s,2H), 6.75 ~7.12-(m,3H), 7.23(s,5H), 7.48(d,J=9Hz,1H), 8.14(d, J=7.9Hz,1H).

(Example 4)

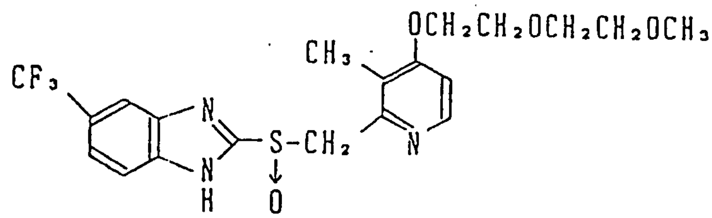
2-[{4-(2-Benzyloxyethoxy)-3-methylpyridine-2-yl}methylsulfinyl]-5-trifluoromethyl-1H-benzimidazole



^{1}H-NMR($CDCl_3$) δ ; 2.18(s,3H), 3.7 ~3.92 (m,2H), 4.1~4.34(m,2H), 4.58(s,2H), 4.78(s,2H), 6.94-(d,J=5.71Hz,1H), 7.32 (s,5H), 7.59(d,J=8.79Hz,1H), 7.83(d, J=8.79Hz,1H), 7.99(s,1H), 8.17(d,J=5.71Hz,1H)

(Example 5)

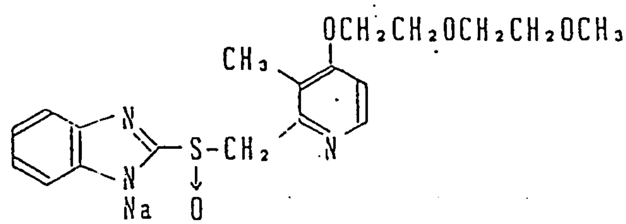
2-[{4-(2-(2-Methoxyethoxy))ethoxy-3-methylpyridine-2-yl}methylsulfinyl]-5-trifluoromethyl-1H-benzimidazole



^{1}H-NMR($CDCl_3$) δ ; 2.19(s,3H), 3.38(s,3H), 3.4~4.3(m,8H), 4.78(ABq,J = 13.6Hz, Δ ν = 12.5Hz,2H), 6.72-(d,J = 5.62Hz,1H), 7.49 (d,J = 9Hz,1H), 7.64(d,J = 9Hz,1H), 8.02 (bs,1H), 8.26(d,J = 5.62Hz,1H)

Example 6

Sodium salt of 2-[{4-(2-(2-methoxyethoxy))ethoxy-3-methylpyridene-2-yl}methylsulfinyl]-1H-benzimidazole



0.45 g of 2[{4-(2-(2-methoxyethoxy))ethoxy-3-methylpyridine-2-yl}methylthio]benzimidazole was dissolved in 40 ml of dichloromethane to obtain a solution. 0.22 g of m-chloroperbenzoic acid was added to this solution in portions at -40 °C, followed by the addition of 0.16 g of triethylamine. The obtained mixture was heated to 0 °C, followed by the addition of 20 ml of a 1N aqueous solution of sodium hydrogencarbonate. The obtained mixture was stirred for 30 minutes and extracted with dichloromethane. The extract was dried over magnesium sulfate and distilled to remove the dichloromethane. 12.1 ml of a 0.1N aqueous solution of sodium hydroxide was added to the obtained residue. The obtained mixture was stirred at a room temperature for one hour, followed by the addition of absolute ethanol. The obtained mixture was evaporated under a reduced pressure to dryness. The obtained residue was crystallized from an ethanol/ether mixture to obtain 0.42 g of the title sodium salt.

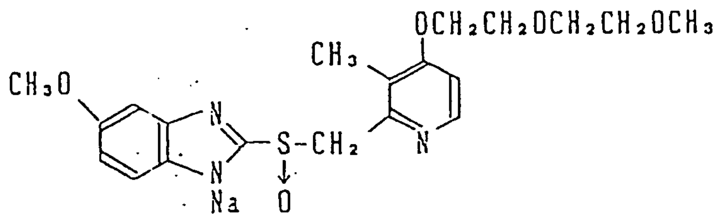
^{1}H-NMR(DMSO-d_6) δ ; 2.16(s,3H), 3.25(s,3H), 3.3 ~3.9(m,6H), 4.0~4.14(m,2H), 4.55 (ABq,J = 13.18Hz, Δ ν = 13.55Hz,2H), 6.8~ 6.9(m,3H), 7.4~7.5(dd,J = 6.15Hz,3.08Hz, 2H), 8.28(d,J = 5.27Hz,1H)

Examples 7 to 10

The following compounds were prepared in a similar manner to that described in Example 6.

(Example 7)

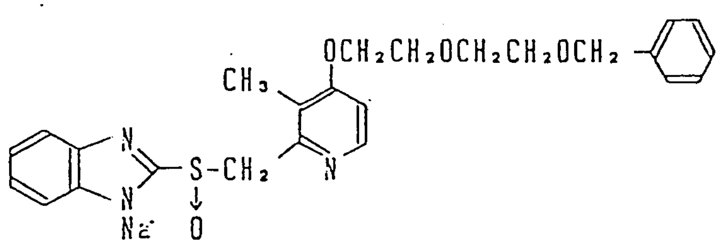
Sodium salt of 5-methoxy-2-[{4-(2-(2-methoxyethoxy))ethoxy-3-methylpyridine-2-yl}methylsulfinyl]-1H-benzimidazole



^{1}H-NMR(CD_3OD) δ ; 2.14(s,3H), 3.34(s,3H), 3.6(m,4H), 3.84(s,5H), 4.18(m,2H), 6.76-(dd,J = 9.36Hz,2.52Hz,1H), 6.9(d,J = 5.76Hz,1H), 7.14(d,J = 2.52Hz,1H), 7.5 (d,J = 9.36Hz,1H), 8.26-(d,J = 5.76Hz,1H)

(Example 8)

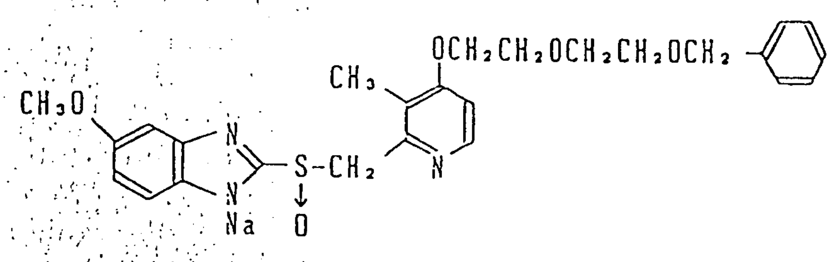
Sodium salt of 2-[{4-(2-(2-benzyloxyethoxy))ethoxy-3-methylpyridine-2-yl}methylsulfinyl]-1H-benzimidazole



^{1}H-NMR(DMSO-d_6) δ ; 2.16(s,3H), 3.4~3.9 (m,6H), 3.96~4.28(m,2H), 4.49(s,2H), 4.6(ABq,J = 12.6Hz, $\Delta\nu$ = 12.85Hz,2H), 6.8 ~7.2(m,3H), 7.29(s,5H), 7.5(dd, J = 6.16Hz,3.08Hz,2H), 8.25(d,J = 5.71Hz, 1H)

(Example 9)

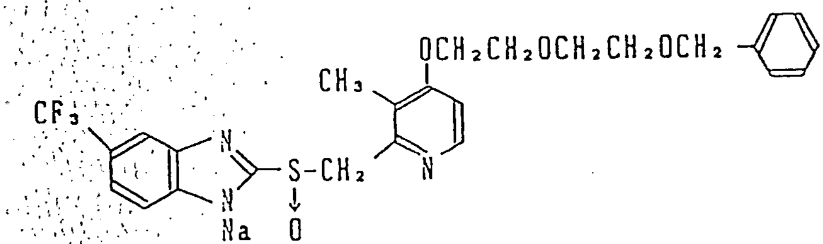
Sodium salt of 2-[{4-(2-(2-benzyloxyethoxy))ethoxy-3-methylpyridine-2-yl}methylsulfinyl]-5-methoxybenzimidazole



^{1}H-NMR(DMSO-d_6) δ ; 2.16(s,3H), 3.63(m, 4H), 3.74(s,3H), 3.85(m,2H), 4.18(m, 2H), 4.49(s,2H), 4.55-(ABq,J = 13.18Hz, Δ ν = 13.55Hz,2H), 6.6(dd,J = 9.35Hz,3.20 Hz,1H), 7.03(d,J = 2.63Hz,1H), 6.89(d, J = 5.72Hz,1H), 8.26(d,J = 5.72Hz,1H)

(Example 10) :

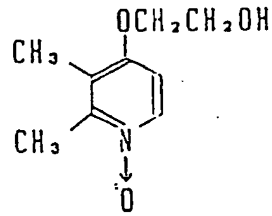
Sodium salt of 2-[{4-(2-(2-benzyloxyethoxy))ethoxy-3-methylpyridine-2-yl}methylsulfinyl]-5-trifluoromethylbenzimidazole



^{1}H-NMR(DMSO-d_6) δ ; 2.16(s,3H), 3.62(m,4H), 3.79(m,2H), 4.19(m,2H), 4.48(s,2H), 4.57(ABq,J = 13.18Hz, Δ ν = 12.29Hz,2H), 6.93(d,J = 5.71Hz,1H), 7.16(dd,J = 8.35Hz, 1.75Hz,1H), 7.29(s,5H), 7.62(d,J = 8.35 Hz,1H), 7.83(s,1H), 8.28(d,J = 5.71 Hz, 1H)

Preparative Example 4

4-(2-Hydroxyethoxy)-2,3-dimethylpyridine N-oxide



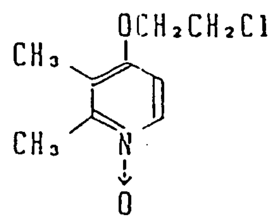
4.60 g (0.2 mol) of metallic sodium was dissolved in 80 ml of ethylene glycol under cooling with ice to obtain a solution. This solution was stirred in a nitrogen atmosphere at 100 °C for one hour, followed by the addition of 15.76 g (0.1 mol) of 4-chloro-2,3-dimethylpyridine N-oxide at a room temperature. The obtained mixture was stirred at 120 °C for 2 hours. After the completion of the reaction, the reaction mixture was distilled to dryness to remove the ethylene glycol. The obtained residue was purified by silica gel column chromatography (solvent: chloroform/methanol = 19 : 1) to obtain 13.28 g of 4-(2-hydroxyethoxy)-2,3-dimethylpyridine N-oxide as a white crystal.

^{1}H-NMR(CD_3OD) δ ;

2.29(s,3H), 2.55(s,3H), 3.93(t,2H), 4.20 (t,2H), 7.04(d,H), 8.18(d,H)

Preparative Example 5

4-(2-Chloroethoxy)-2,3-dimethylpyridine N-oxide



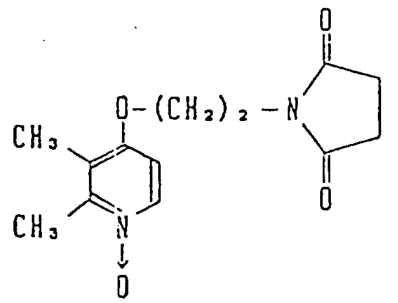
1.0 ml of thionyl chloride was gradually added to a solution of 0.92 g (5 mmol) of 4-(2-hydroxyethoxy)-2,3-dimethylpyridine N-oxide in 10 ml of chloroform under cooling with ice. The obtained mixture was heated under reflux for 2 hours, cooled by allowing to stand, neutralized with a saturated aqueous solution of sodium hydrogencarbonate and extracted with 100 ml of methyl ethyl ketone twice. The extract was dried over magnesium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography (solvnet: chloroform/methanol = 19 : 1) to obtain 0.56 g of 4-(2-chloroethoxy)-2,3-dimethylpyridine N-oxide as a colorless crystal.

^{1}H-NMR($CDCl_3$) δ ;

2.24(s,3H), 2.54(s,3H), 3.86(t,2H), 4.28 (t,2H), 6.62(d,H), 8.17(d,H)

Preparative Example 6

2,3-Dimethyl-4-(2-succinimidoethoxy)pyridine N-oxide



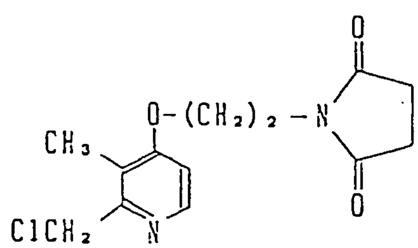
A mixture comprising 0.40 g (2 mmol) of 4-(2-chloroethoxy)-2,3-dimethylpyridine N-oxide, 0.30 g (3 mmol) of succinimide, 0.48 g (3.5 mmol) of potassium carbonate and 30 ml of methyl ethyl ketone was heated under reflux for 2 hours, cooled by allowing to stand and filtered. The filtrate was evaporated to dryness to remove the methyl ethyl ketone. The obtained residue was purified by silica gel column chromatography (solvent: $CHCl_3/MeOH$ = 19 : 1) to obtain 0.12 g of 2,3-dimethyl-4-(2-succinimidoethoxy)-pyridine N-oxide as a white crystal.

^1H-NMR($CDCl_3$) δ ;

2.12(s,3H), 2.49(s,3H), 2.73(s,4H), 3.80 ~4.25(m,4H), 6.51(d,H), 8.03(d,H)

Preparative Example 7

2-Chloromethyl-3-methyl-4-(2-succinimidoethoxy)pyridine



0.12 g of 2,3-dimethyl-4-(2-succinimidoethoxy)pyridine N-oxide was dissolved in 5 ml of acetic anhydride to obtain a solution. This solution was stirred at 100 °C for 0.5 hour and cooled, followed by the addition of 30 ml of ethanol. The obtained mixture was stirred at a room temperature for 0.5 hour and distilled to remove the solvent. Thus, 0.14 g of crude 2-acetoxymethyl-3-methyl-4-(2-succinimidoethoxy)-pyridine was obtained as an oil.

^1H-NMR($CDCl_3$) δ ;

2.10(s,3H), 2.14(s,3H), 2.72(s,4H), 3.72 ~4.24(m,4H), 5.15(s,2H), 6.61(d,H), 8.24 (d,H)

This acetoxymethyl derivative was dissolved as such in 5 ml of 1 N HCl to obtain a solution. This solution was stirred at 100 °C for 0.5 hour, cooled, neutralized with a saturated aqueous solution of sodium hydrogencarbonate and extracted with 100 ml of chloroform twice. The obtained extract was dried over magnesium sulfate and filtered. The filtrate was concentrated to obtain 0.12 g of crude 2-hydroxymethyl-3-methyl-4-(2-succinimidoethoxy)pyridine as a colorless crystal.

^{1}H-NMR($CDCl_3$) δ ;

1.93(s,3H), 2.68(s,4H), 3.80~4.22(m,4H), 4.56(s,2H), 6.59(d,H), 8.21(d,H)

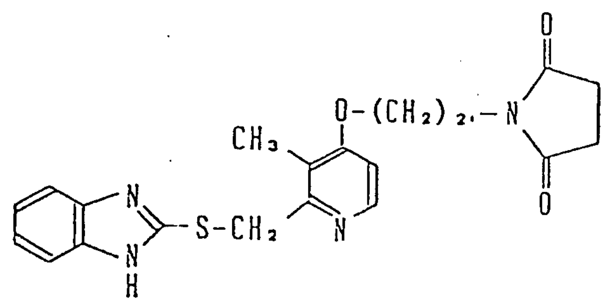
This crude hydroxymethyl derivative was dissolved as such in 5 ml of chloroform to obtain a solution. 0.11 g of thionyl chloride was dropwise added to this solution under cooling with ice. The obtained mixture was heated under reflux for 0.5 hour, cooled, neturalized with a saturated aqueous solution of sodium hydrogencarbonate and extracted with 100 ml of chloroform twice. The obtained extract was dried over magnesium sulfate and filtered. The filtrate was concentrated and dried in a vacuum to obtain 0.07 g of 2-chloromethyl-3-methyl-4-(2-succinimidoethoxy)pyridine as a white semicrystal.

^{1}H-NMR($CDCl_3$) δ ;

2.15(s,3H), 2.68(s,4H), 3.80~4.20(m,4H), 4.60(s,2H), 6.61(d,H), 8.22(d,H)

Example 11

2-[{3-Methyl-4-(2-succinimidoethoxy)pyridine-2-yl}methylthio]-1H-benzimidazole



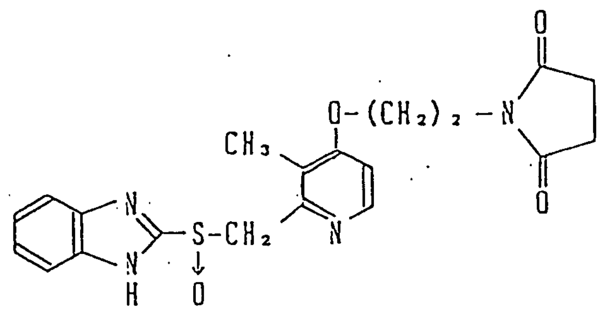
A mixture comprising 0.03 g (0.18 mmol) of 2-mercapto-1H-benzimidazole, 0.06 g (0.21 mmol) of 2-chloromethyl-3-methyl-4-(2-succinimidoethoxy)pyridine, 0.03 g (0.21 mmol) of potassium carbonate and 10 ml of methyl ethyl ketone was heated under reflux in a nitrogen atmosphere for 3 hours, cooled and filtered. The filtrate was concentrated and dried in a vacuum, followed by the addition of water. The obtained mixture was extracted with 50 ml of chloroform thrice. The extract was dried over magnesium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography to obtain 0.08 g of 2-[{3-methyl-4-(2-succinimidoethoxy)pyridine-2-yl}methylthio]-1H-benzimidazole as a white crystal.

^{1}H-NMR($CDCl_3$) δ ;

2.09(s,3H), 2.63(s,4H), 3.72~4.16(m,4H), 4.27(s,2H), 6.53(d,H), 6.90 ~7.50(m,4H), 8.18(d,H)

Example 12

2-[{3-Methyl-4-(2-succinimidoethoxy)pyridine-2-yl}methylsulfinyl]-1H-benzimidazole



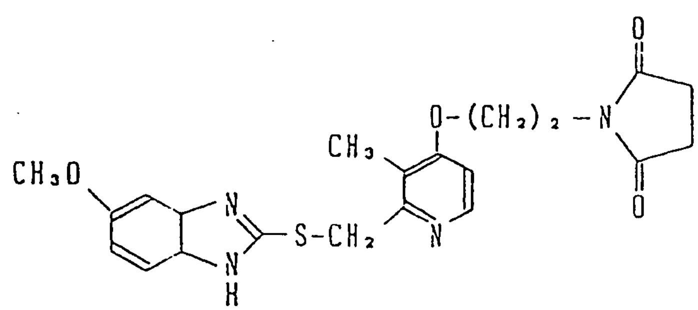
0.18 g of 95% m-chloroperbenzoic acid was gradually added to a solution of 0.40 g (1 mmol) of 2-[{3-methyl-4-(2-succinimidoethoxy)pyridine-2-}yl-methylthio]-1H-benzimidazole in 20 ml of dichloromethane at -60°C to obtain a mixture. This mixture was stirred for 0.5 hour, followed by the addition of 0.15 g of triethylamine. The obtained mixture was heated to -10°C, followed by the addition of 30 ml of a saturated aqueous solution of sodium hydrogen-carbonate. The obtained mixture was stirred for 0.5 hour and extracted with 50 ml of dichloromethane twice. The extract was dried over magnesium sulfate and filtered. The filtrate was concentrated and dried in a vacuum to obtain a crude product. This crude product was crystallized from dichloromethane/diethyl ether to obtain 0.36 g of 2-[{3-methyl-4-(2-succinimidoethoxy)-pyridine-2-yl}methylsufinyl]-1H-benzimidazole as a white crystal.

^{1}H-NMR($CDCl_3$) δ ;

2.12(s,3H), 2.73(s,4H), 3.83~4.29(m,4H), 4.56~4.92(m,2H), 6.65(d,H), 7.17 ~7.72 (m,4H), 8.25(d,H)

Example 13

5-Methoxy-2-[{3-methyl-4-(2-succinimidoethoxy)pyridine-2-yl}methylthio]-1H-benzimidazole



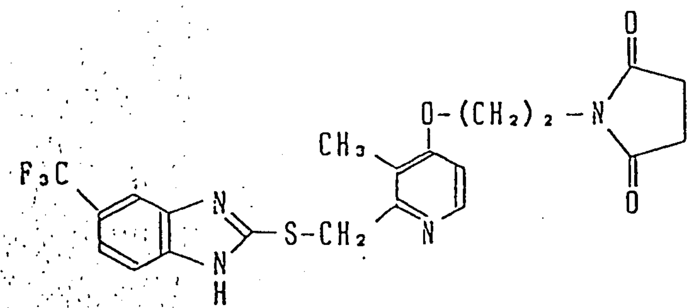
The title compound was prepared in a similar manner to that described in Example 11.

^{1}H-NMR($CDCl_3$) δ ;

2.20(s,3H), 2.74(s,4H), 3.84(s,3H), 3.88 ~4.38(m,4H), 4.35(s,2H), 6 71(d,H), 6.80 ~7.48(m,3H), 8.35(d,H)

Example 14

2-[{3-Methyl-4-(2-succinimidoethoxy)pyridine-2-yl}methylthio]-5-trifluoromethyl-1H-benzimidazole



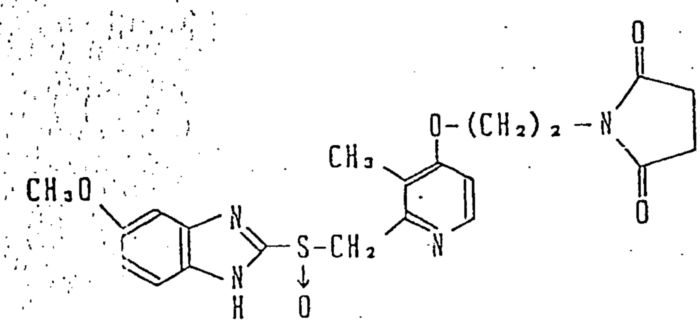
The title compound was prepared in a similar manner to that described in Example 11.

^{1}H-NMR(CDCl$_3$) δ ;

2.22(s,3H), 2.75(s,4H), 3.88~4.08(m,2H), 4.08~4.28(m,2H), 4.45(s,2H), 6.73(d,H), 7.32~7.86(m,3H), 8.32(d,H)

Example 15

5-Methoxy-2-[{3-methyl-4-(2-succinimidoethoxy)pyridine-2-yl}methylsulfinyl]-1H-benzimidazole



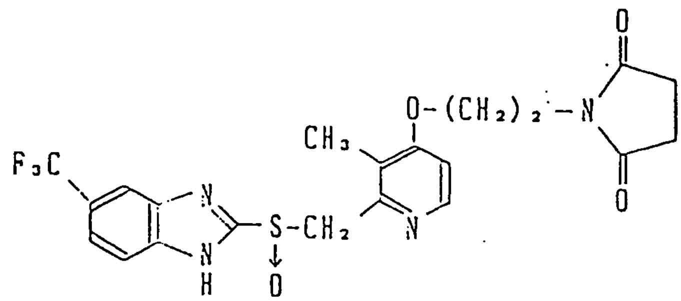
The title compound was prepared in a similar manner to that described in Example 12.

^{1}H-NMR(CDCl$_3$) δ ;

2.13(s,3H), 2.74(s,4H), 3.86(s,3H), 3.60 ~4.30(m,4H), 4.50~4.90(m,2H), 6.65(d,H), 6.80~7.68(m,3H), 8.25(d,H)

Example 16

2-[{3-Methyl-4-(2-succinimidoethoxy)pyridine-2-yl}methylsulfinyl]-1H-5-trifluoromethylbenzimidazole



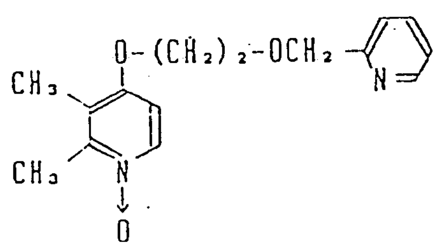
The title compound was prepared in a similar manner to that described in Example 12.

^{1}H-NMR($CDCl_3$) δ ;

2.23(s,3H), 2.75(s,4H), 3.80~4.45(m,4H), 4.67(m,2H), 6.74(d,H), 7.30 ~8.00(m,3H), 8.37(d,H)

Preparative Example 8

2,3-Dimethyl-4-(2-pyridylmethoxyethoxy)pyridine N-oxide



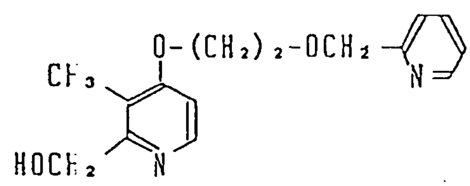
0.39 g of 60% sodium hydride was added to a suspension of 1.20 g (6.5 mmol) of 4-(2-hydroxyethoxy)-2,3-dimethylpyridine N-oxide in 40 ml of tetrahydrofuran under cooling with ice in a nitrogen atmosphere to obtain a mixture. This mixture was stirred for 0.5 hour, followed by the addition of 0.83 g (6.5 mmol) of 2-chloromethylpyridine. The obtained mixture was heated under reflux for 8 hours, cooled and filtered. The filtrate was concentrated and purified by silica gel column chromatography (solvent: ethyl acetate/n-hexane = 4 : 1 ~ $CHCl_3$/MeOH = 19 : 1) to obtain 0.61 g of 2,3-dimethyl-4-(2-pyridylmethoxyethoxy)pyridine N-oxide.

^{1}H-NMR($CDCl_3$) δ ;

2.20(s,3H), 2.50(s,3H), 3.80~4.04(m,2H), 4.04~4.28(m,2H), 4.70(s,2H), 6.60(d,H), 7.00~7.74(m,3H), 8.04(d,H), 8.45(d,H)

Preparative Example 9

2-Hydroxymethyl-3-methyl-4-(2-pyridylmethoxyethoxy)pyridine

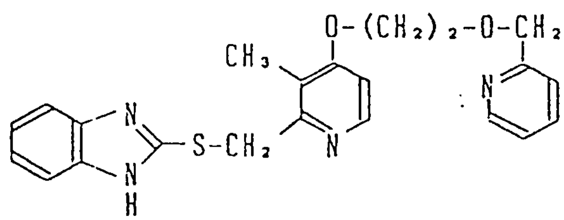


A mixture comprising 0.60 g of 2,3-dimethyl-4-(2-pyridylmethoxyethoxy)pyridine N-oxide and acetic anhydride was stirred at 100°C for 0.5 hour and cooled, followed by the addition of 40 ml of ethanol. The obtained mixture was stirred at a room temperature for 0.5 hour and distilled to remove the solvent. The residue was dried in a vacuum to obtain 0.47 g of crude 2-acetoxymethyl-3-methyl-4-(2-pyridylmethoxyethoxy)pyridine as an oil.

This crude intermediate was dissolved as such in 1N HCl to obtain a solution. This solution was stirred at 100°C for one hour, cooled, neutralized with a saturated aqueous solution of sodium hydrogencarbonate and extracted with 50 ml of dichloromethane twice. The extract was dried over magnesium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography (solvent: ehtyl acetate) to obtain 0.40 g of 2-hydroxymethyl-3-methyl-4-(2-pyridylmethoxyethoxy)pyridine as a colorless semicrystal.

Example 17

2-[{3-Methyl-4-(2-pyridylmethoxyethoxy)pyridine-2-yl}methylthio]-1H-benzimidazole



0.71 g (6 mmol) of thionyl chloride was added to a solution of 0.40 g (1.5 mmol) of 2-hhdroxymethyl-3-methyl-4-(2-pyridylmethoxyethoxy)pyridine in 10 ml of chloroform under cooling with ice to obtain a mixture. This mixture was stirred at 0°C for 2 hours. After the completion of the reaction, the mixture was neutralized with a saturated aqueous solution or sodium hydrogencarbonate and extracted with 50 ml of chloroform four times. The extract was dried over magnesium sulfate and filtered. The obtained filtrate was concentrated and dried in a vacuum to obtain 0.42 g of crude 2-chloromethyl-3-methyl-4-(2-pyridylmethoxyethoxy)pyridine as a semicrystal.

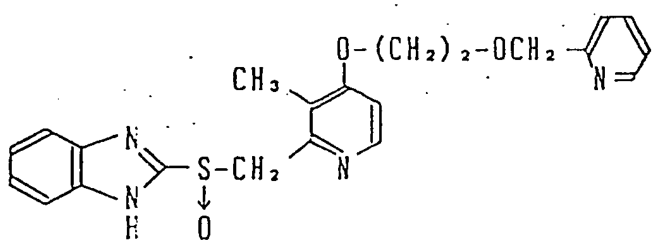
A mixture comprising 0.40 g of this crude intermediate, 0.18 g of 2-mercapto-1H-benzimidazole, 0.19 g of potassium carbonate and 30 ml of methyl ethyl ketone was heated under reflux in a nitrogen atmosphere for 2 hours, cooled and filtered. The filtrate was concentrated and purified by silica gel column chromatography (solvent: ethyl acetate/n-hexane) to obtain 0.38 g of 2-[{3-methyl-4-(2-pyridylmethoxyethoxy)-pyridine-2-yl}methylthio]-1H-benzimidazole as a colorless oil.

^{1}H-NMR($CDCl_3$) δ ;

2.26(s,3H), 3.80~4.04(m,2H), 4.10~4.28 (m,2H), 4.35(s,2H), 4.70(s,2H), 6.70(d,H), 6.94~7.20(m,7H), 8.25(d,H), 8.45(d,H)

Example 18

2-[{3-Methyl-4-(2-pyridylmethoxyethoxy)pyridine-2-yl}methylfulfinyl]-1H-benzimidazole



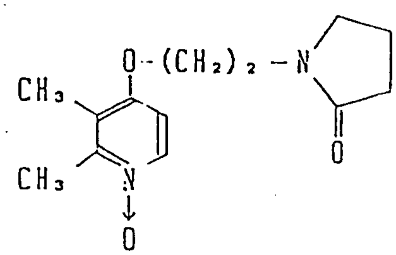
0.16 g of m-chloroperbenzoic acid was added to a solution of 0.38 g of 2-[{3-methyl-4-(2-pyridylmethoxyethoxy)pyridine-2-yl}methylthio]-1H-benzimidazole in 20 ml of dichloromethane at -60°C in a nitrogen atmosphere to obtain a mixture. This mixture was stirred for 0.5 hour. After the completion of the reaction, 0.16 g of triethylamine was added to the reaction mixture. The obtained mixture was heated to -10°C, followed by the addition of 30 ml of a saturated aqueous solution of sodium hydrogencarbonate. The obtained mixture was stirred at a room temperature for 0.5 hour and extracted with 50 ml of dichloromethane thrice. The extract was dried over magnesium sulfate and filtered. The filtrate was concentrated and dried in a vacuum to obtain a crude product. This crude product was crystallized from dichloromethane/diethyl ether to obtain 0.31 g of 2-[{3-methyl-4-(2-pyridylmethoxyethoxy)pyridine-2-yl}methylsulfinyl]-1H-benzimidazole as a white crystal.

^{1}H-NMR($CDCl_3$) δ ;

2.17(s,3H), 3.83~4.06(m,2H), 4.06~4.34 (m,2H), 4.72(s,2H), 4.64~4.84(m,2H), 6.70-(d,H), 7.04 ~7.80(m,7H), 8.27(d,H), 8.55(d,H)

Preparative Example 10

2,3-Dimethyl-4-[2-(2-pyrrolidone)ethoxy]pyridine N-oxide



0.42 g of sodium hydride was added to 30 cc of N,N-dimethylformamide at a room temperature to obtain a mxiture. This mixture was cooled to 0°C, followed by the addition of 0.74 g of 2-pyrrolidone. The obtained mixture was stirred at 80°C for 1.5 hours and cooled to a room temperature, followed by the addition of 1.17 g of 4-(2-chloroethoxy)-2,3-dimethylpyridine N-oxide. The obtained mixture was stirred at 60 to 80°C for 5 hours and cooled, followed by the addition of 20 cc of a saturated aqueous solution of sodium hydrogencarbonate. The obtained mixture was extracted with chloroform. The extract was dried over magnesium sulfate and filtered. The filtrate was concentrated to obtain a crude product. This crude product was purified by silica gel column chromatography to obtain 430 mg of 2,3-dimethyl-4-[2-(2-pyrrolidone)-ethoxy]pyridine N-oxide as a yellow crystal.

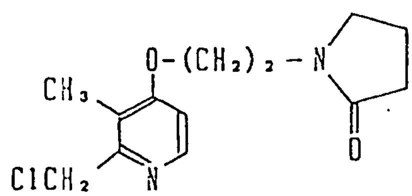
^{1}H-NMR($CDCl_3$) δ ;

2.2(s,3H), 2.54(s,3H), 1.9~2.5(m,4H), 3.57(t,J=7Hz,2H), 3.73(t,J=6Hz,2H), 4.16

(t,J = 6Hz,2H), 6.65(d,J = 7Hz,1H), 8.15(d,J = 7Hz,1H)

Preparative Example 11

2-Chloromethyl-3-methyl-4-[2-(2-pyrrolidone)ethoxy]pyridine



10 cc of acetic anhydride was added to 0.65 g of 2,3-dimethyl-4-[2-(2-pyrrolidone)ethoxy]pyridine N-oxide at a room temperature to obtain a mixture. This mixture was stirred at 90 °C for 2 hours, followed by the addition of ethanol. The obtained mixture was distilled under a reduced pressure to obtain 0.79 g of crude 2-acetoxymethyl-3-methy-4-[2-(2-pyrrolidone)ethoxy]pyridine.

20 cc of 1N HCl was added to this crude intermediate to obtain a mixture. This mixture was stirred at 100 °C for 2 hours, cooled, neutralized with a saturated aqueous solution of sodium hydrogencarbonate and extracted with chloroform. The extract was dried over magnesium sulfate and filtered. The filtrate was distilled under a reduced pressure to obtain 510 mg of crude 2-hydroxymethyl-3-methyl-4-[2-(2-pyrrolidone)ethoxy]pyridine as an ocherous crystal.

^{1}H-NMR(CDCl$_3$) δ ;

2.04(s,3H), 1.9 ~2.6(m,4H), 3.58(t,J = 7 Hz,2H), 3.73(t,J = 6Hz,2H), 4.2-(t,J = 6Hz,2H), 4.65(s,2H), 6.7(d,J = 7HZ,1H), 8.3(d,J = 7Hz, 1H)

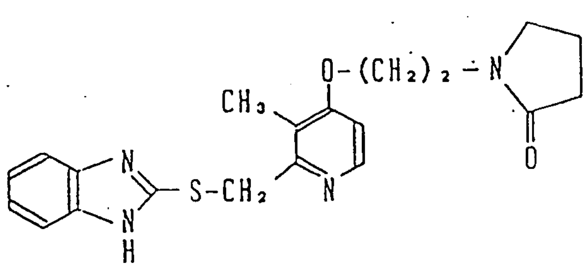
500 mg of this crude intermediate was dissolved in 10 ml of dichloromethane to obtain a solution. 1.19 g of thionyl chloride was dropwise added to this solution at -20 °C. The obtained mixture was stirred at a room temperature for 30 minutes, neutralized with a saturated aqueous solution of sodium hydrogencarbonate and extracted with chloroform. The extract was dried over magnesium sulfate and filtered. The filtrate was distilled under a reduced pressure to obtain 0.57 mg of crude 2-chloromethyl-3-methyl-4-[2-(2-pyrrolidone)ethoxy]pyridine as an oil.

^{1}H-NMR(CDCl$_3$) δ ;

2.25(s,3H), 1.8 ~2.5(m,4H), 3.54(t,J = 7 Hz,2H), 3.68(t,J = 6Hz,2H), 4.1-(t,J = 6Hz,2H), 6.62(d,J = 6Hz,1H), 8.22(d,J = 6Hz,1H)

Example 19

2-[3-Methyl-4{2-(2-pyrrolidone)ethoxy}pyridine-2-yl]methylthio-1H-benzimidazole



20 cc of methyl ethyl ketone was added to a mixture comprising 0.55 g of 2-chloromethyl-3-methyl-4-[2-(2-pyrrolidone)ethoxy]pyridine, 0.3 g of 2-mercapto-1H-benzimidazole and 0.33 g of potassium carbonate, to obtain a mixture. This mixture was heated under reflux for 2 hours and filtered. The filtrate was

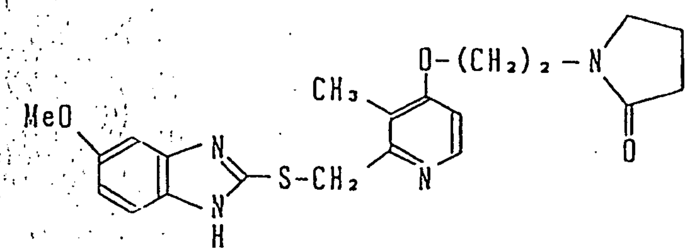
concentrated to obtain a crude product. This crude product was purified by silica gel column chromatography to obtain 0.27 g of the title compound as a pale yellow crystal.

^{1}H-NMR(CDCl$_3$) δ ;

2.26(s,3H), 1.8 ~2.5(m,4H), 3.57(t, J=7 Hz,2H), 3.7(t,J=6Hz,2H), 4.13(t,J=6Hz,2H), 4.34(s,2H), 6.66(d,J=6Hz,1H), 7.0 ~7.55 (m,4H), 8.25(d,J=6Hz,1H)

Example 20

5-Methoxy-2-[3-methyl-4-{2-(2-pyrrolidone)ethoxy}pyridine-2-yl]methylthio-1H-benzimidazole



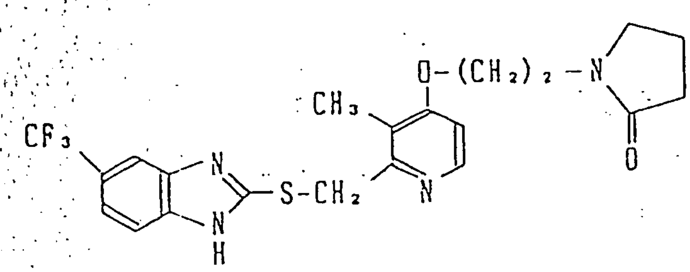
The title compound was prepared in a similar manner to that described in Example 19.

^{1}H-NMR(CDCl$_3$) δ ;

2.24(s,3H), 1.9 ~2.5(m,4H), 3.56(t,J=7 Hz,2H), 3.72(t,J=6Hz,2H), 3.83(s,3H), 4.17(t,J=6Hz,2H), 4.4(s,2H), 6.6~7.5(m, 4H), 8.35(d,J=6Hz,1H)

Example 21

2-[3-Methyl-4-{2-(2-pyrrolidone)ethoxy}pyridine-2-yl]methylthio-5-trifluoromethyl-1H-benzimidazole



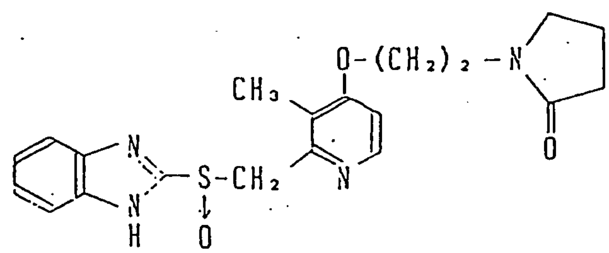
The title compound was prepared in a similar manner to that described in Example 19.

^{1}H-NMR(CDCl$_3$) δ ;

2.28(s,3H), 1.9 ~2.55(m,4H), 3.57(t,J=7 Hz,2H), 3.74(t,J=6Hz,2H), 4.2(t,J=6Hz,2H), 4.4(s,2H), 6.77(d,J=6Hz,1H), 7.27~7.85 (m,3H), 8.38(d,J=6Hz,1H)

Example 22

2-[3-Methyl-4-{2-(2-pyrrolidonethoxy}pyridine-2-yl]methylsulfinyl-1H-benzimidazole



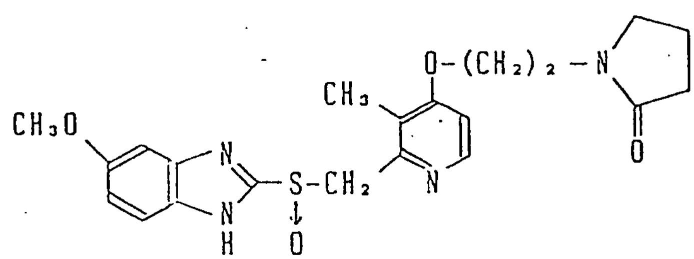
0.27 g of 2-[3-methyl-4-{2-(2-pyrrolidone(ethoxy}pyridine-2-yl]methylthio-1H-benzimidazole was dissolved in 20 ml of dichloromethane to obtain a solution. 0.12 g of 95% m-chloroperbenzoic acid was added to this solution at -60 °C. The obtained mixture was stirred at -50 to -40 °C for 4 hours, followed by the addition of 0.09 g of triethylamine and a saturated aqueous solution of sodium hydrogencarbonate. The obtained mixture was extracted with dichloromethane. The extract was dried over magnesium sulfate and filtered. The filtrate was concentrated to obtain a crude product. This crude product was crystallized from dichloromethane/ether to obtain 0.18 g of the title compound.

^{1}H-NMR(CDCl$_3$) δ ;

2.18(s,3H), 1.9 ~2.5(m,4H), 3.53(t,J=7 Hz,2H), 3.73(t,J=6Hz,2H), 4.16(t,J=6Hz,2H), 4.74(ABq, J=14Hz, Δ ν=16Hz,2H), 6.7(d, J=6 Hz,1H), 7.2 ~7.7(m,4H), 8.25-(d,J=6Hz, 1H)

Example 23

5-Methoxy-2-[3-methyl-4-{2-(2-pyrrolidone)ethoxy}pyridine-2-yl]methylsulfinyl-1H-benzimidazole



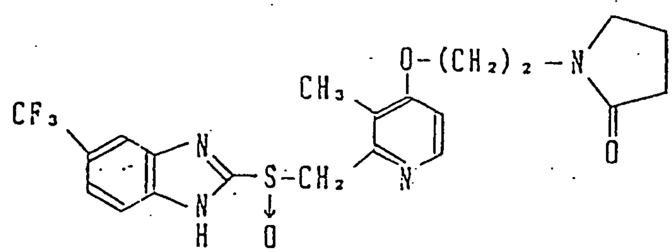
The title compound was prepared in a similar manner to that described in Example 22.

^{1}H-NMR(CDCl$_3$) δ ;

2.17(s,3H), 1.9 ~2.5(m,4H), 3.38 ~3.78 (m,4H), 3.8(s,3H), 4.1(t;J=6Hz,2H), 4.66 (ABq,J=13Hz, Δ ν=12.4Hz,2H), 6.6(d,J=6Hz, 1H), 6.77~7.6(m,3H), 8.17-(d,J=6Hz,1H)

Example 24

2-[3-Methyl-4-{2-(2-pyrrolidone)ethoxy}pyridine-2-yl]methylsulfinyl-5-trifluoromethyl-1H-benzimidazole



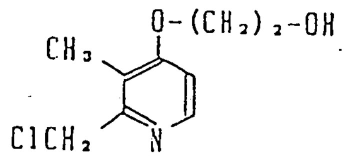
The title compound was prepared in a similar manner to that described in Example 22.

^{1}H-NMR($CDCl_3$) δ ;

2.17(s,3H), 1.8 ~2.55(m,4H), 3.4 ~3.8 (m,4H) 4.75(ABq,J=14.3Hz, Δν=17.5Hz,2H), 6.69(d,J=6Hz,1H), 7.24~8.0(m,3H), 8.2 (d,J=6Hz,1H)

Preparative Example 12

2-Chloromethyl-4-(2-hydroxyethoxy)-3-methylpyridine



15 ml of acetic anhydride was added to 25 g of 4-(2-hydroxyethoxy)-2,3-dimethylpyridine N-oxide to obtain a solution. This solution was stirred at 90°C for 2 hours, followed by the addition of ethanol. The obtained mixture was distilled under a reduced pressure to obtain 4-(2-acetoxyethoxy)-2-acetoxymethyl-3-methylpyridine.

20 g of sodium hydroxide, 20 ml of water and 50 ml of ethanol were added to this intermediate to obtain a mixture. This mixture was stirred at a room temperature for 10 minutes and distilled to remove the ethanol, followed by the addition of 50 ml of a saturated aqueous solution of common salt. The obtained mixture was extracted with 2-butanone. The extract was dried over magnesium sulfate and filtered. The filtrate was distilled under a reduced pressure to obtain 20 g of 4-(2-hydroxyethoxy)-2-hydroxymethyl-3-methylpyridine.

^{1}H-NMR($CDCl_3$) δ ;

2.02(s,3H), 3.9 ~4.2(m,4H), 4.50(s,2H), 6.63(d,J=6Hz,1H), 8.15(d,J=6Hz,1H)

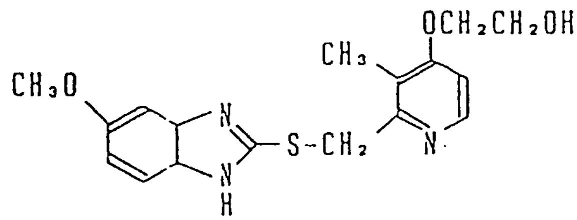
11.9 g of the 4-(2-hydroxyethoxy)-2-hydroxymethyl-3-methylpyridine prepared above was dissolved in 200 ml of dichloromethane to obtain a solution. 24 ml of thionyl chloride was dropwise added to this solution at 0°C. The obtained mixture was stirred at a room temperature for 2 hours and distilled under a reduced pressure to remove the dichloromethane and excess thionyl chloride. A saturated aqueous solution of sodium hydrogencarbonate was added to the residue to obtain a mixture. This mixture was extracted with chloroform. The extract was dried over magnesium sulfate and filtered. The filtrate was concentrated to obtain 10.9 g of 2-chloromethyl-4-(2-hydroxyethoxy)-3-methylpyridine.

^{1}H-NMR($CDCl_3$) δ ;

2.3(s,3H), 3.9~4.2(m,4H), 4.69(s,2H), 6.73(d,J=6Hz,1H), 8.3(d,J=6Hz,1H)

Example 25

2-[4-(2-Hydroxyethoxy)-3-methylpyridine-2-yl]methylthio-5-methoxy-1H-benzimidazole



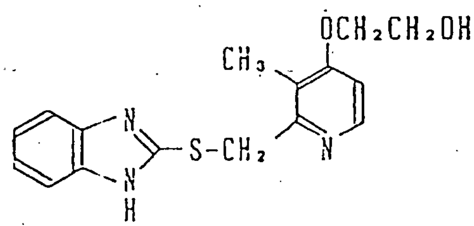
60 ml of ethanol was added to a mixture comprising 0.7 g of 2-chloromethyl-4-(2-hydroxyethoxy)-3-methylpyridine, 0.63 g of 2-mercapto-5-methoxy-1H-benzimidazole and 0.16 g of sodium hydroxide to obtain a mixture. This mixture was stirred at 60°C for one hour, concentrated and purified by silica gel column chromatography to obtain 1.08 g of the title compound.

^{1}H-NMR(DMSO-d_6) δ ;

2.2(s,3H), 3.72(s,3H), 3.6~4.1(m,4H), 4.6(s,2H), 6.6~7.35(m,4H), 8.14(d,J=6Hz, 1H)

Example 26

2-[4-(2-Hydroxyethoxy)-3-methylpyridine-2-yl]methylthio-1H-benzimidazole



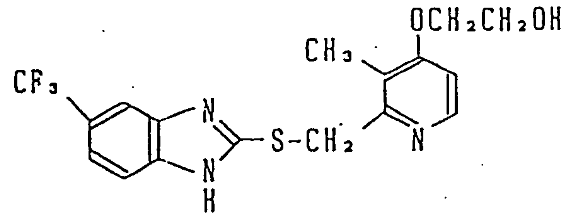
The title compound was prepared in a similar manner to that described in Example 25.

^{1}H-NMR(DMSO-d_6) δ ;

2.24(s,3H), 3.6 ~4.18(m,4H), 4.7(s,2H), 6.93(d,J=6Hz,1H), 7.0 ~7.6(m,4H), 8.25 (d,J=6Hz,1H)

Example 27

2-[4-(2-Hydroxyethoxy)-3-methylpyridine-2-yl]methylthio-5-trifluoromethyl-1H-benzimidazole



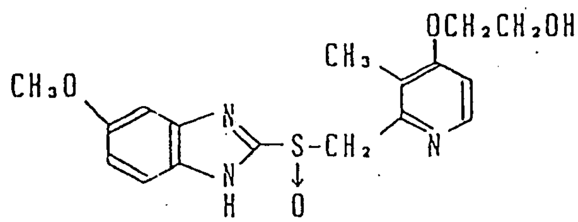
The title compound was prepared in a similar manner to that described in Example 25.

^{1}H-NMR(DMSO-d_6) δ ;

2.25(s,3H), 3.6 ~4.2(m,4H), 4.75(s,2H), 6.96(d,J=6Hz,1H), 7.3 ~7.9(m,3H), 8.25 (d,J=6Hz,1H)

Example 28

2-[4-(2-Hydroxyethoxy)-3-methylpyridine-2-yl]methylsulfinyl-5-methoxy-1H-benzimidazole



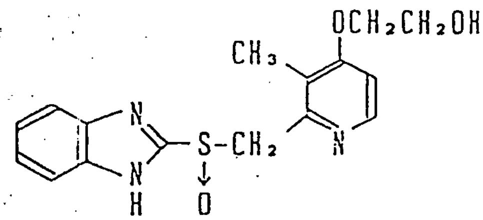
0.9 g of 2-[4-(2-hydroxyethoxy)-3-methylpyridine-2-yl]methylthio-5-methoxy-1H-benzimidazole was dissolved in a mixture comprising 5 ml of methanol and 80 ml of dichloromethane to obtain a solution. 0.51 g of m-chloroperbenzoic acid was added to this solution at -60°C. The obtained mixture was stirred at -50 to -40°C for 4.5 hours, followed by the addition of 0.38 g of triethylamine. A saturated aqueous solution of sodium hydrogencarbonate was added to the obtained mixture and the resulting mixture was extracted with chloroform. The extract was dried over magnesium sulfate and filtered. The filtrate was distilled under a reduced pressure to obtain a crude product. This crude product was crystallized from dichloromethane/isopropyl ether to obtain 0.58 g of the title compound.

^{1}H-NMR(DMSO-d_6) δ ;

2.17(s,3H) 3.8(s,3H), 3.6~4.18(m,4H), 4.73(ABq,J=14Hz, $\Delta\nu$=8Hz,2H), 6.8 ~7.6(m, 4H),8.21(d,J=6Hz,1H)

Example 29

2-[4-(2-Hydroxyethoxy)-3-methylpyridine-2-yl]methylsulfinyl-1H-benzimidazole



The title compound was prepared in a similar manner to that described in Example 28.

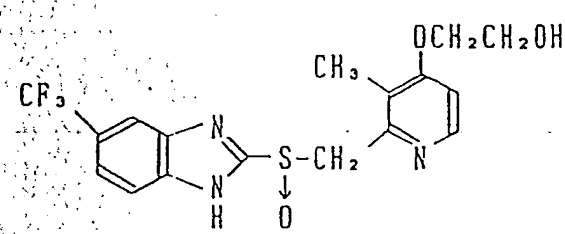
M^{+1} :332

^{1}H-NMR(DMSO-d_6) δ ;

2.17(s,3H), 3.6 ~4.2(m,4H), 4.74(s,2H), 6.95(d,J=6Hz,1H), 7.18~7.77(m,4H), 8.22 (d,J=6Hz,2H)

Example 30

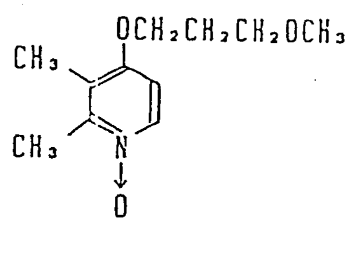
2-[4-(2-Hydroxyethoxy)-3-methylpyridine-2-yl]methylsulfinyl-5-trifluoromethyl-1H-benzimidazole



The title compound was prepared in a similar manner to that described in Example 28.

Preparative Example 13

4-(3-Methoxypropoxy)-2,3-dimethylpyridine N-oxide



2.0 g (22 mmol) of 3-methoxypropanol was dissolved in 50 ml of dimethyl sulfoxide to obtain a solution. 2.7 g (66 mmol) of sodium hydride was added to this solution at a room temperature. The obtained mixture was stirred at 60°C for one hour and cooled to a room temperature by allowing to stand, followed by the addition of 3.0 g (19 mmol) of 4-chloro-2,3-dimethylpyridine N-oxide. The obtained mixture was stirred at

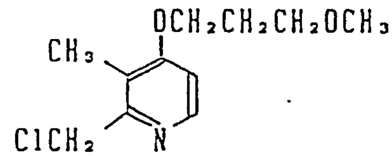
40 °C for one hour. After the completion of the reaction, the reaction mixture was distilled to remove the dimethyl sulfoxide. The obtained residue was purified by silica gel column chromatography to obtain 760 mg of 4-(3-methoxypropoxy)-2,3-dimethylpyridine N-oxide.

^{1}H-NMR($CDCl_3$) δ ;

2.1(m,2H), 2.2(s,3H), 2.54(s,3H), 3.35(s, 3H), 3.55(t,J=6Hz,2H), 4.1(t,J=6Hz,2H), 6.65(d,J=7.4Hz,1H), 8.16(d,J=7.4Hz,1H)

Preparative Example 14

2-Chloromethyl-4-(3-methoxypropoxy)-3-methylpyridine



20 ml of acetic anhydride was added to 760 mg (3.6 mmol) of 4-(3-methoxypropoxy)-2,3-dimethylpyridine N-oxide to carry out the reaction at 90 °C for one hour. The reaction mixture was distilled to remove the acetic anhydride, followed by the addition of a saturated aqueous solution of sodium hydrogencarbonate. The obtained mixture was extracted with chloroform. The extract was concentrated to obtain 700 mg of 2-acetoxymethyl-4-(3-methoxypropoxy)-3-methylpyridine as a brown oil.

500 mg of sodium hydroxide and 15 cc of ethanol were added to the 2-acetoxymethyl-4-(3-methoxypropoxy)-3-methylpyridine prepared above. The obtained mixture was stirred at 50 °C for one hour. After the completion of the reation, the reaction mixture was distilled to remove the ethanol, followed by the addition of water. The obtained mixture was extracted with chloroform. The obtained chloroform layer was concentrated to obtain 450 mg of 2-hydroxymethyl-4-(3-methoxypropoxy)-3-methylpyridineas a brown oil.

^{1}H-NMR($CDCl_3$) δ ;

2.04(s,3H), 2.1(m,2H), 3.35(s,3H), 3.56(t, J=5.7Hz,2H), 4.12(t,J=5.7Hz,2H), 4.64-(s, 2H), 6.J(d,J=7Hz,1H), 8.24(d,J=7Hz,1H)

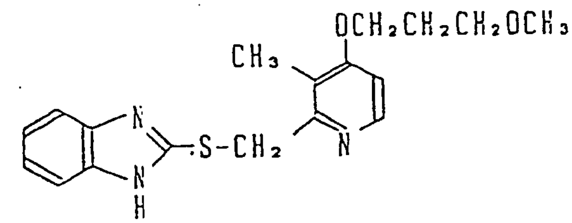
450 mg of the 2-hydroxymethyl-4-(3-methoxypropoxy)-3-methylpyridineprepared above was dissolved in 20 ml of dichloromethane to obtain a solution. 760 mg of thionyl chloride was dropwise added to this solution at 0 °C. The obtained mixture was stirred at a room temperature for 2 hours. After the completion of the reaction, the reaction mixture was distilled to remove the dichloromethane and the thionyl chloride. A saturated aqueous solution of sodium hydrogencarbonate was added to the obtained residue. The obtained mixture was extracted with chloroform. The obtained chloroform layer was concentrated to obtain 470 mg of 2-chloromethyl-4-(3-methoxypropoxy)-3-methylpyridine as a brown crystal.

^{1}H-NMR($CDCl_3$) δ ;

2.1(m,2H), 2.27(s,3H), 3.36(s,3H), 3.56(t, J=5.7Hz,2H), 4.12(t,J=5.7Hz,2H), 4.69-(s, 2H), 6.71(d,J=7Hz,1H), 8.26(d,J=7Hz,1H)

Example 31

2-[{4-(3-Methoxypropoxy)-3-methylpyridine-2-yl}methylthio]-1H-benzimidazole



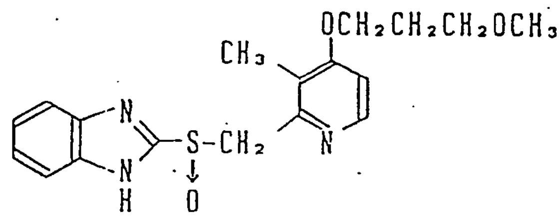
20 cc of ethanol was added to a mixture comprising 280 mg (1.8 mmol) of 2-mercapto-1H-benzimidazole, 470 mg (2 mmol) of 2-chloromethyl-4-(3-methoxypropoxy)-3-methylpyridine and 100 mg (2.4 mmol) of sodium hydroxide. The obtained mixture was stirred at 50 °C for 3 hours. After the completion of the reaction, the reaction mixture was distilled to remove the ethanol. The obtained residue was purified by silica gel column chromatography to obtain 590 mg of 2-[{4-(3-methoxypropoxy)-3-methylpyridine-2-yl}methylthio]-1H-benzimidazole as a pale yellow crystal.

^{1}H-NMR(CDCl$_3$) δ ;

2.09(t,J=6.1Hz,2H), 2.26(s,3H), 3.35(s,3H), 3.56(t,J=6.1Hz,2H), 4.13-(t,J=6.1Hz,2H), 4.37(s,2H), 6.76(d,J=6.1Hz,1H), 7.1 ~7.25, (m,2H), 7.5(br,s,2H), 8.33(d,J=6.1Hz,1H)

Example 32

2-{4-(3-Methoxypropoxy)-3-methylpyridine-2-yl}methylsulfinyl-1H-benzimidazole



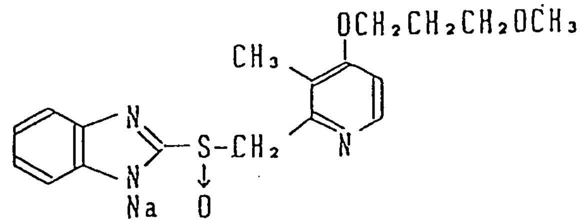
5 g of 2-[{4-(3-methoxypropoxy)-3-methylpyridine-2-yl}methylthio]-1H benzimidazole was dissolved in a mixture comprising 100 ml of dichloromethane and 25 ml of diethyl ether to obtain a solution. 2.83 g of 85% m-chloroperbenzoic acid was added to this solution in portions at -45 °C. After the completion of the reaction, 2 g of triethylamine was added to the reaction mixture and the obtained mixture was heated to -10 °C, followed by the addition of 50 ml of 1N sodium hydroxide. The obtained mixture was stirred at a room temperature for 30 minutes. The obtained aqueous layer was washed with 20 ml of dichloromethane twice and adjusted to pH 11 with a 2 M aqueous solution of ammonium acetate. The aqueous layer was extracted with 50 ml of dichloromethane thrice. The obtained dichloromethane layer was washed with 50 ml of a saturated aqueous solution of sodium hydrogencarbonate twide, dried over magnesium sulfate and distilled to remove the dichloromethane. The obtained oily product was crystallized from dichloromethane/ether to obtain 4.17 g of the title compound as a white crystal. M.p.: 99 to 100 °C (dec.).

^{1}H-NMR(CDCl$_3$) δ ;

1.83~2.09(m,2H), 2.13(s,3H), 3.34(s,3H), 3.52(t,J=6.2Hz,2H), 4.05(t,J=6.2Hz,2H), 4.79(s,2H), 6.70(d,J=5.7Hz,1H), 7.07~ 7.30(m,2H), 7.30~7.60(br,s,2H), 8.27(d, J=5.7Hz,1H)

Example 33

Sodium salt of 2-[{4-(3-methoxypropoxy)-3-methylpyridine-2-yl}methylsulfinyl]-1H-benzimidazole



500 mg (1.46 mmol) of 2-[{4-(3-methoxypropoxy)-3-methylpyridine-2-yl}methylthio]-1H-benzimidazole was dissolved in 20 cc of dichloromethane to obtain a solution. 320 mg of 85% m-chloroperbenzoic acid was added to this solution in portions at -45°C. After the completion of the reaction, 370 mg of triethylamine was added to the reaction mixture. The obtained mixture was heated to -10°C, followed by the addition of 30 ml of a saturated aqueous solution of sodium carbonate. The obtained mixture was stirred at a room temperature for 30 minutes and extracted with dichloromethane. The extract was dried over magnesium sulfate and distilled to remove the dichloromethane. Thus, a crude product was obtained. This crude product was dissolved in 14.6 cc of a 0.1 N aqueous solution of sodium hydroxide to obtain a solution. This solution was distilled together with 30 cc of ethanol thrice to remove the water as an azeotropic mixture with ethanol and dried in a vacuum. Ether was added to the obtained residue to precipitate a white crystal. This crystal was washed with ether thrice by decantation and dried in a vacuum to obtain 530 mg of sodium salt of 2-[{4-(3-methoxypropoxy)-3-methylpyridine-2-yl}methylsulfinyl]-1H-benzimidazole.

M.p.: 140 to 141°C (dec.).

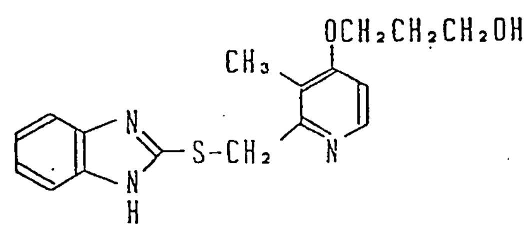
M^{+1} : 382

^{1}H-NMR(DMSO-d_6) δ ;

1.99(t,J=6.1Hz,2H), 2.17(s,3H), 3.25(s,3H), 3.49(t,J=6.1Hz,2H), 4.09-(t,J=6.1Hz,2H), 4.56(ABq,J=14.1Hz, $\Delta\nu$=21.3Hz,2H), 6.8~ 6.9(m,3H), 7.4~7.5(m,2H), 8.27(d,J=5.7Hz, 1H)

Example 34

2-[{4-(3-Hydroxypropoxy)-3-methylpyridine-2-yl}methylthio]-1H-benzimidazole



80 ml of ethanol was added to a mixture comprising 1.39 g (9.27 mmol) of 2-mercaptobenzimidazole, 2.0 g (9.27 mmol) of 2-chloromethyl-4-(3-hydroxypropoxy)-3-methylpyridineand 0.44 g (11.1 mmol) of sodium hydroxide. The obtained mixture was stirred at 50°C for one hour. After the completion of the reaction, the reaction mixture was concentrated. The obtained residue was purified by silica gel column chromatography to obtain 1.7 g of the title compound (56%).

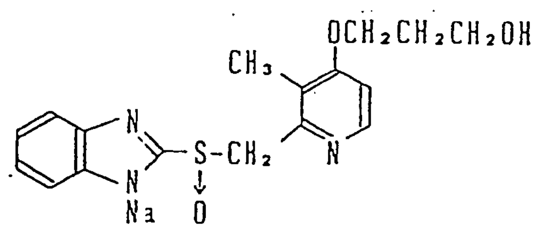
M^{+1} : 368

^{1}H-NMR(DMSO-d_6) δ ;

1.8 ~2.1(m,2H), 2.24(s,3H), 3.6(t,J=6Hz, 2H), 4.2(t,J=6Hz,2H), 4.7(s,2H), 7.0~7.38 (m,3H), 7.38~7.6(m,2H), 8.35(d,J=6Hz,1H)

Example 35

Sodium salt of 2-[{4-(3-hydroxypropoxy)-3-methylpyridine-2-yl}methylsulfinyl]-1H-benzimidazole



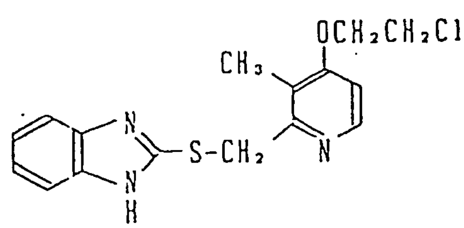
1.0 g (3.04 mmol) of 2-[{4-(3-hydroxypropoxy)-3-methylpyridine-2-yl}methylthio]-1H-benzimidazole was dissolved in 100 ml of dichloromethane to obtain a solution. 580 mg of 90% m-chloroperbenzoic acid was added to this solution at -45 °C. The obtained mixture was stirred for 2 hours. After the completion of the reaction, 470 mg of triethylamine was added to the reaction mixture. The obtained mixture was heated to -20 °C, followed by the addition of 30 ml of a saturated aqueous solution of sodium hydrogencarbonate. The obtained mixture was stirred at a room temperature for 30 minutes and extracted with chloroform. The obtained chloroform layer was concentrated to obtain a crude product. This crude product was crystallized from dichloromethane/ether to obtain 830 mg of 2-[{4-(3-hydroxypropoxy)-3-methylpyridine-2-yl}methylsufinyl]-1H-benzimidazole. This product was dissolved in 24 ml of 0.1 N aqueous sodium hydroxide. The obtained solution was distilled together with ethanol to remove the water as an azeotropic mixture with ethanol and dried under vacuumizing with a vacuum pump. Ether was added to the obtained residue to precipitate a colorless crystal. This crystal was separated by filtration. Thus, 860 mg of the title compound was obtained (77%).

^{1}H-NMR(DMSO-d_6) δ ;

1.7 ~2.1(m,2H), 2.16(s,3H), 3.58(t,J=6Hz, 2H), 4.12(t,J=6Hz,2H), 4.55-(ABq,J=13Hz, $\Delta\nu$=20Hz,2H), 6.7~7.0(m,3H), 7.3~7.6(m, 2H), 8.27-(d,J=6Hz,1H)

Example 36

2-[{4-(2-Chloroethoxy)-3-methylpyridine-2-yl}methylthio]-1H-benzimidazole

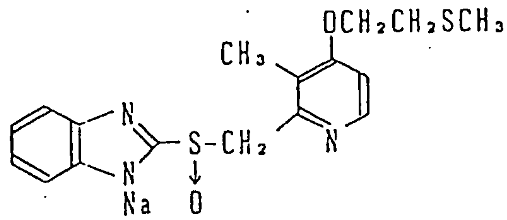


12.3 g of crude 2-mercaptobenzimidazole, 20 g of 4-(2-chloroethoxy)-2-chloromethyl-3-methylpyridine hydrochloride and 11 g of sodium hydroxide were dissolved in 300 ml of ethanol to obtain a solution. This solution was stirred at 60 °C for 2 hours and distilled under a reduced pressure to remove the ethanol. The obtained residue was chromatographed over a silica gel column and eluted with 40% ethyl acetate in hexane and then with ethyl acetate to obtain 15.5 g of the title compound as a white solid.

^{1}H-NMR($CDCl_3$) δ ;2.24(3H,s,CH_3), 3.80(2H, t,J=4Hz,CH_2), 4.20(2H,t,J=4Hz,CH_2), 4.40(2H,s,CH_2), 6.82-(1H,d,J=6Hz,Py-H), 7.00~7.40(4H,m,Ar-H), 8.28(1H,d,J=6Hz, Py-H)

Example 37

Sodium salt of 2-[{4-(2-methylthioethoxy)-3-methylpyridine-2-yl}methylsulfinyl]-1H-benzimidazole



0.50 g of the thio ether prepared in Example 35 was dissolved in 20 ml of dichloromethane to obtain a solution. 0.36 g of m-chloroperbenzoic acid was added to this solution in portions at -50 to -40 °C. After the completion of the reaction, 0.21 g of triethylamine was added to the reaction mixture at the same temperature. The obtained mixture was heated to -20 °C, followed by the addition of 28 ml of a 1N aqueous solution of sodium hydrogencarbonate. The obtained mixtures was stirred for 30 minutes and extracted with dichloromethane. The extract was washed with a saturated aqueous solution of common salt, dried over magnesium sulfate and distilled to remove the dichloromethane.

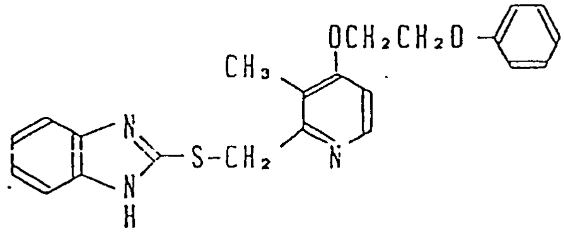
The obtained crude sulfoxide was dissolved in 10 ml of ethanol, followed by the addition of 1 g of a 15% aqueous solution of sodium methylmercaptide. The obtained mixture was stirred at 80 °C for 4 hours and distilled to remove the solvent. The residue was chromatographed over a silica gel column and eluted with 2% methanol in chloroform containing 1% of triethylamine and then with 10% methanol in chloroform to obtain a purification product. 7.2 ml of 1N aqueous sodium hydroxide and 20 ml of ethanol were added to this product. The obtained mixture was evaporated to dryness under a reduced pressure to obtain 460 mg of the title compound.

M^{+1} : 384

^{1}H-NMR(DMSO-d_6) δ ; 2.18(3H,s,CH_3), 2.90 (2H,t,J=7Hz,CH_2), 4.24(2H,t,J=7Hz,CH_2), 4.78(2H,s,CH_2), 6.80~7.60(4H,m,Ar-H), 6.98(1H,d,J=6Hz,Py-H), 8.30(1H,d,J=6Hz, Py-H)

Example 38

2-[{4-(2-Phenoxyethoxy)-3-methylpyridine-2-yl}methylthio]-1H-benzimidazole

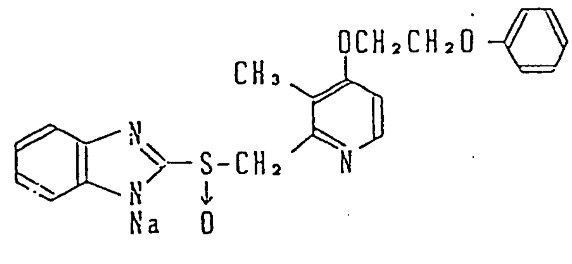


A mixture comprising 1.0 g of [4-(2-phenoxyethoxy)-3-methylpyridine-2-yl]methanol, 0.60 ml of thionyl chloride and 12 ml of dichloromethane was kept at 40 °C for 60 minutes to carry out the reaction. The reaction mixture was distilled to remove the solvent. Thus, a brown syrupy residue was obtained. 50 ml of ethanol, 0.70 g of sodium hydroxide and 1.2 g of 2-mercaptobenzimidazole were added to the residue. The obtained mixture was heated at 70 °C for two hours and distilled to remove the ethanol. The obtained residue was chromatographed over a silica gel column and eluted with 30% ethyl acetate in hexane and

then with ethyl acetate to obtain 1.2 g of the title compound as a white solid.
^{1}H-NMR(DMSO-d_6) δ ; 2.22(3H,s), 4.40(2H,s,), 4.70(2H,s), 6.86~7.52(10H,m), 8.28(1H, d,J=6Hz)

Example 39

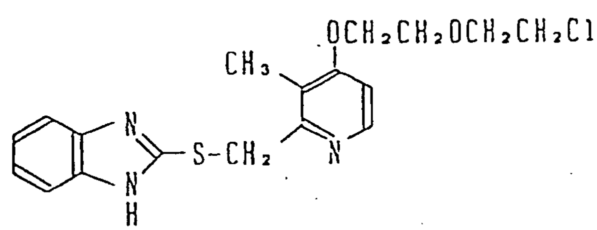
Sodium salt of 2-[{3-methyl-4-(2-phenoxyethoxy) pyridine-2-yl}methylsulfinyl]-1H-benzimidazole

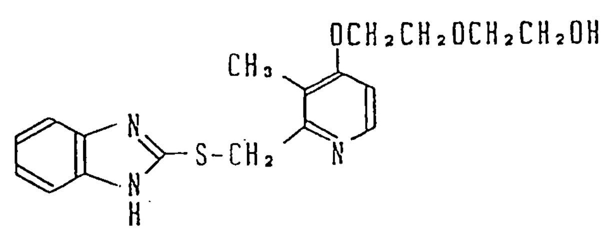


0.70 g of the thio ether prepared in Example 37 was dissolved in 200 ml of dichloromethane to obtain a solution. 0.39 g of m-chloroperbenzoic acid was added to this solution in portions at -30 to -40 °C. After the completion of the reaction, 0.12 g of triethylamine was added to the reaction mixture at the same temperature. The obtained mixture was heated to -10 °C, followed by the addition of 10 ml of a saturated aqueous solution of sodium hydrogencarbonate. The obtained mixture was stirred at -10 to 10 °C for 30 minutes. The obtained dichloromethane layer was washed with a saturated aqueous solution of sodium hydrogencarbonate, dried over magnesium salfate and distilled to remove the dichloromethane. The obtained residue was dissolved in a mixture comprising 20 ml of ethanol and 1.8 ml of 1N aqueous sodium hydroxid to obtain a solution. This solution was evaporated to dryness under a reduced pressure. The residue was crystallized from ethanol/ether to obtain 0.61 g of the title compound as a light brown solid.
^{1}H-NMR(DMSO-d_6) δ ; 2.17(3H,s), 4.32(4H,s,), 4.36(1H,d,J=13Hz), 4.68(1H,d,J=13Hz), 6.74~7.44(10H,m), 8.22(1H,d,J=6Hz)

Example 40

2-[{4-(2-(2-Chloroethoxy)-3-methylpyridine-2-yl}methylthio]-1H-benzimidazole and 2-[{4-(2-(2-hydroxyethoxy)ethoxy)-3-methylpyridine-2-yl}methylthio]-1H-benzimidazole





0.54 g of sodium hydroxide was added to an ethanolic solution of 3.1 g of a crude mixture comprising 4-[2-(2-chloroethoxy)ethoxy]-2-chloromethyl-3-methylpyridine and 2-chloromethyl-4-[2-(2-hydroxyethoxy)-ethoxy]-3-methylpyridine which has been prepared by the chlorination of 2-hydroxymethyl-4-[2-(2-hydroxyethoxy)ethoxy]-3-methylpyridine and 2.0 g of 2-mercapto-1H-benzimidazole to obtain a mixture. This mixture was stirred at 60 °C for 1.5 hour, cooled and distilled under a reduced pressure to remove the ethanol. The obtained residue was chromatographed over a silica gel column and eluted with ethyl acetate/n-hexane and then with methanol/ethyl acetate to obtain 1.0 g of 2-[{4-(2-(2-chloroethoxy)ethoxy)-3-methylpyridine-2-yl}methylthio]-1H-benzimidazole

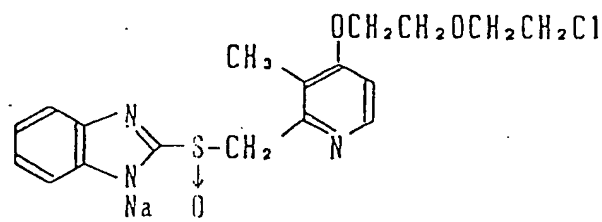
^{1}H-NMR ($CDCl_3$) δ ; 2.28(s,3H), 3.56~4.04(m, 6H), 4.04 ~4.32 m,2H), 4.4(s,2H), 6.76 (d,J=6Hz,1H), 7.08~7.32(m,3H), 7.4 ~ 7.68(m,2H), 8.36(d,J=6Hz,1H)

and 1.9 g of 2-[{4-(2-(2-hydroxyethoxy)ethoxy)-3-methylpyridine-2-yl}methylthio]-1H-benzimidazole.

^{1}H-NMR($CDCl_3$) δ ; 2.24(s,3H), 3.56~4.28(m, 8H), 4.4(s,2H), 6.12(d,J=7Hz,1H), 7.04~ 7.32(m,2H), 7.4 ~7.68-(m,2H), 8.32(d,J =7Hz,1H)

Example 41

Sodium salt of 2-[{4-(2-(2-chloroethoxy)ethoxy)-3-methylpyridine-2-yl}methylsulfinyl]-1H-benzimidazole

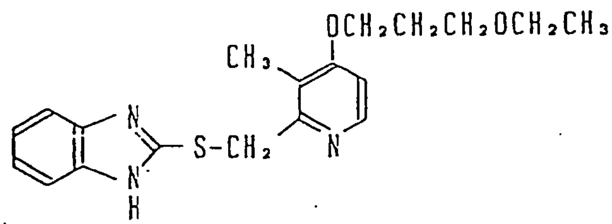


0.57 g of m-chloroperbenzoic acid was added in portions to a solution of 1.0 g of 2-[{4-(2-(2-chloroethoxy)ethoxy)-3-methylpyridine-2-yl}methylthio]-1H-benzimidazole in 80 ml of dichloromethane under stirring and dehumidifying at -50 °C. The obtained mixture was stirred for 2 hours and heated to -30 °C, followed by the addition of 0.51 g of triethylamine at the same temperature. The obtained mixture was made basic with a 2N aqueous solution of sodium carbonate at -10 °C and extracted with dichloromethane. The extract was dried over magnesium sulfate and distilled to remove the dichloromethane. Thus, 1.0 g of a residue was obtained. This residue was dissolved in 26 ml of 0.1N aqueous sodium hydroxide, followed by the addition of ethanol. The obtained mixture was distilled under a reduced pressure. Ethanol was added to the obtained residue and the obtained mixture was again distilled under a reduced pressure to obtain a residue. Ether was added to this residue to obtain 1.07 g of a crystal.

^{1}H-NMR(DMSO-d_6) δ ; 2.17(s,3H), 3.56~3.96 (m,6H), 4.0~4.28(m,2H), 4.04(d,J=12.6Hz, 1H),4.68-(d,J=12.6Hz,1H), 6.76 ~8.04(m, 3H), 7.36 ~7.6(m,2H), 8.26(d,J=6Hz,1H)

Example 42

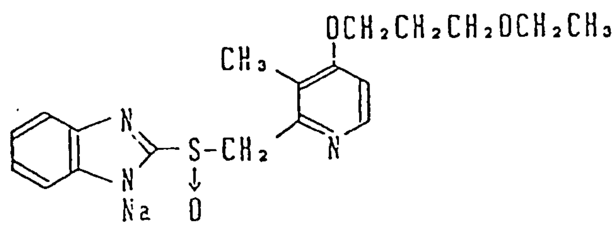
2-[{4-(3-Ethoxy)propoxy-3-methylpyridine-2-yl}methylthio]-1H-benzimidazole



A mixture comprising 4.2 g of {4-(3-ethoxypropoxy)-3-methylpyridine-2-yl}methyl methanesulfonate, 1.87 g of 2-mercaptobenzimidazole and 30 ml of ethanol was stirred at a room temperature for one hour and distilled to remove the ethanol. The obtained residue was purified by silica gel column chromatography to obtain 0.88 g of the title compound and 5.1 g of methanesulfonate of the title compound.
^{1}H-NMR($CDCl_3$) δ ; 1.19(t,J=7.0Hz,3H), 1.9 ~2.1(m,2H), 2.24(s,3H), 3.48(q,J=7.0 Hz,2H), 3.58-(t,J=6.2Hz,2H), 4.11(t,J= 6.2Hz,2H), 4.38(s,2H), 6.73(d,J=5.7Hz, 1H), 6.97 ~7.20(m,2H), 7.32~7.55(m, 2H), 8.31(d,J=5.7Hz,1H)

Example 43

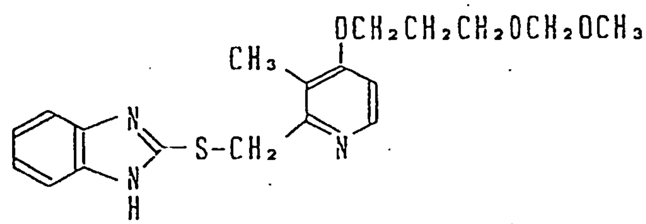
Sodium salt of 2-[{4-(3-ethoxypropoxy)-3-methylpyridine-2-yl}methylsulfinyl]-1H-benzimidazole



0.6 g of 2-[{4-(3-ethoxypropoxy)-3-methylpyridine-2-yl}methylthio]-1H-benzimidazole was dissolved in 30 ml of dichloromethane to obtain a solution. 0.37 g of 85% m-chloroperbenzoic acid was added to this solution at -45 °C. After 2 hours, 0.43 g of triethylamine was added to the obtained mixture, followed by the addition of 30 ml of a saturated aqueous solution of sodium hydrogencarbonate. The obtained mixture was vigorously stirred at a room temperature for one hour and extracted with dichloromethane. The extract was dried over magnesium sulfate and filtered. The filtrate was concentrated to obtain a residue. This residue was dissolved in 16 ml of 0.1N aqueous sodium hydroxide and the obtained solution was distilled to remove the water. The residue was dried under a reduced pressure and crystallized from ether to obtain 0.54 g of the title compound.
^{1}H-NMR(DMSO-d_6) δ ; 1.11(t,J=7.0Hz,3H), 1.7 ~2.1(m,2H), 2.15(s,3H), 3.2~3.6(m,4H), 3.65(s,3H), 4.09-(t,J=6.2Hz,2H), 4.49 (ABq,J=11.8Hz, $\Delta\nu$=17.0Hz,2H), 6.65 ~ 7.0(m,3H), 7.2~7.6(m,2H), 8.2(d,J=5.6 Hz,1H)

Example 44

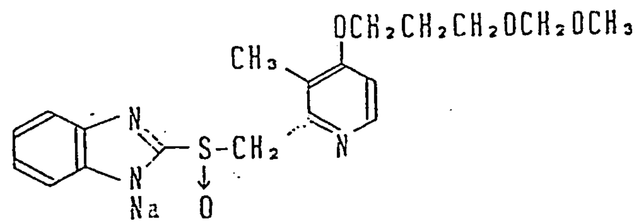
2-[{4-(3-Methoxymethoxy)propoxy-3-methylpyridine-2-yl}methylthio]-1H-benzimidazole



A mixture comprising 1.8 g of {4-(3-methoxymethoxy)propoxy-3-methylpyridine-2-yl}methyl methanesulfonate, 0.76 g of 2-mercaptobenzimidazole, 0.29 g of sodium hydroxide and 50 ml of ethanol was stirred at a room temperature for one hour and distilled to remove the ethanol. The obtained residue was purified by silica gel column chromatography to obtain 1.4 g of the title compound.
^{1}H-NMR($CDCl_3$) δ ; 1.9 ~2.2(m,2H), 2.26(s, 3H), 3.33(s,3H), 3.73(t,J=6.1Hz,2H), 4.16(t,J=6.1Hz,2H), 4.38-(s,2H), 4.62(s, 3H), 6,76(d,J=5.7Hz,1H), 7.0~7.2(m,2H), 7.3 ~7.6(m,2H), 8.34(d,J=5.7Hz,1H)

Example 45

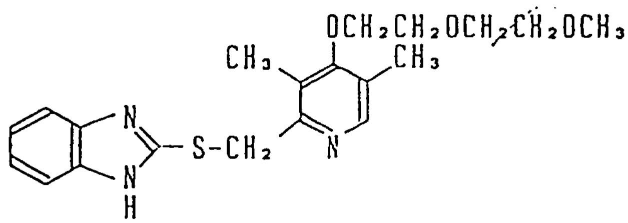
Sodium salt of 2-[{4-(3-methoxymethoxy)propoxy-3-methylpyridine-2-yl}methylsulfinyl]-1H-benzimidazole



0.6 g of 2-[{4-(3-methoxymethoxy)propoxy-3-methylpyridine-2-yl}methylthio]-1H-benzimidazole was dissolved in 40 ml of dichloromethane to obtain a solution. 0.35 g of 85% m-chloroperbenzoic acid was added to this solution at -45 °C. After 2 hours, 0.64 g of triethylamine was added to the mixture at -30 °C, followed by the addition of 40 ml of a saturated aqueous solution of sodium hydrogencarbonate. The obtained mixture was vigorously stirred at a room temperature for 30 minutes and extracted with dichloromethane. The extract was dried over magnesium sulfate and filtered. The filtrate was concentrated to obtain a residue. This residue was dissolved in 14.4 ml of 0.1N aqueous sodium hydroxide to obtain a solution. This solution was distilled to remove the water and the residue was dried under a reduced pressure and crystallized from ether to obtain 0.57 g of the title compound.
^{1}H-NMR(DMSO-d_6) δ ; 1.9 ~2.2(m,2H), 2.17 (s,3H), 3.22(s,3H), 3.63(t,J=5.7Hz,2H), 4.12(t,J=5.7Hz,2H), 4.56(s,2H), 4.41~ 4.85(2H), 6.84~7.1(m,3H), 7.4~7.62(m, 2H), 8.26(d,J=6.1Hz,1H)

Example 46

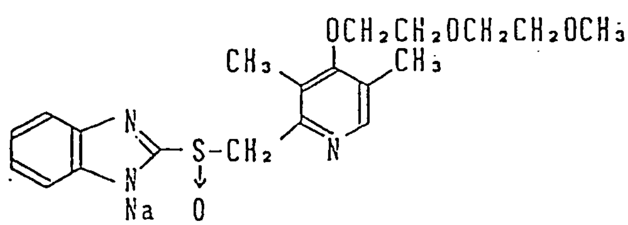
2-[{4-(2-Methoxyethoxy)ethoxy-3,5-dimethylpyridine-2-yl}methylthio]-1H-benzimidazole



A mixture comprising 3.0 g of {4-(2-methoxyethoxy)ethoxy-3,5-dimethylpyridine-2-yl}methyl methanesulfonate, 1.17 g of 2-mercaptobenzimidazole and 30 ml of ethanol was stirred at a room temperature for one hour and distilled to remove the ethanol. The residue was purified by silica gel column chromatography to obtain 0.8 g of the title compound.
^{1}H-NMR($CDCl_3$) δ ; 2.28(s,3H), 2.33(s,3H), 3.37(s,3H), 3.5 ~3.9(m,6H), 3.9~4.2 (m,2H), 4.37(s,2H), 7.1 ~7.3-(m,2H), 7.3 ~7.65(m,2H), 8.24(s,1H)

Example 47

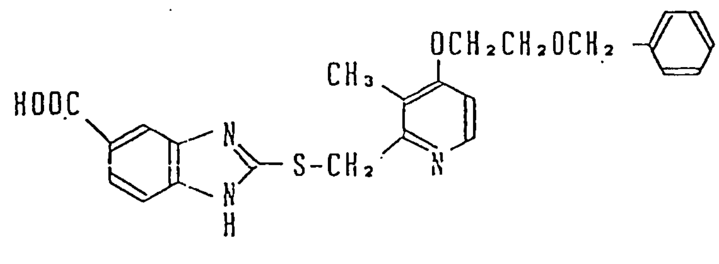
Sodium salt of 2-[{4-(2-methoxyethoxy)ethoxy-3,5-dimethylpyridine-2-yl}methylsulfinyl]-1H-benzimidazole



0.5 g of 2-[{4-(2-methoxyethoxy)ethoxy-3,5-dimethylpyridine-2-yl}methylthio]-1H-benzimidazole was dissolved in 30 ml of dichloromethane to obtain a solution. 0.29 g of 85% m-chloroperbenzoic acid was added to this solution at -45°C. After 2 hours, 0.34 g of triethylamine was added to the obtained mixture, followed by the addition of 30 ml of a saturated solution of sodium carbonate. The obtained mixture was vigorously stirred at a room temperature for one hour and extracted with dichloromethane. The extract was dried over magnesium sulfate and filtered. The filtrate was concentrated to obtain a residue. This residue was dissolved in 12 ml of 0.1N aqueous sodium hydroxide to obtain a solution. This solution was distilled to remove the water. The obtained residue was dried under a reduced pressure and crystallized from ether to obtain 0.57 g of the title compound.
^{1}H-NMR(DMSO-d_6) δ ; 2.21(s,6H), 3.25(s,3H), 3.3 ~3.7(m,6H), 3.7~4.0(m,2H), 4.39 (ABq,J=13.2Hz, $\Delta\nu$=20.7Hz,2H), 6.65 ~ 6.9(m,2H), 7.2~7.5(m,2H), 8.21(s,1H)

Example 48

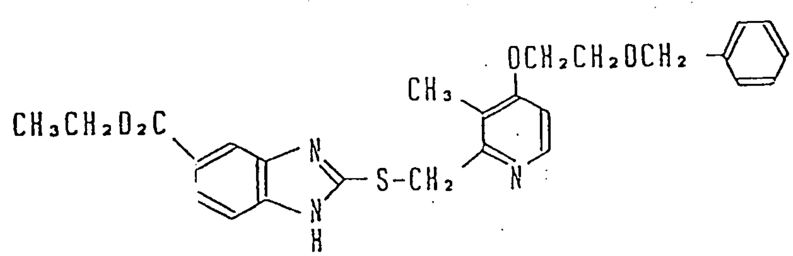
5-Carboxy-2-[{4-(2-benzyloxy)ethoxy-3-methylpyridine-2-yl}methylthio]-1H-benzimidazole



A mixture comprising 1.26 g of 5-carboxy-2-mercaptobenzimidazole, 1.8 g of 4-(2-benzyloxyethoxy)-2-chloromethyl-3-methylpyridine, 0.57 g of sodium hydroxide and 150 ml of methanol was stirred at 50 °C for 1.5 hours and distilled under a reduced pressure to remove the methanol. The obtained residue was purified by silica gel column chromatography and recrystallized from a methanol/ethyl acetate mixture to obtain 1.52 g of the title compound.
^{1}H-NMR(DMSO-d_6) δ ; 2.25(s,3H), 3.65~3.9 (m,2H), 4.1 ~4.3(m,2H), 4.58(s,2H), 4.74(s,2H), 6.95-(d,J=5.7Hz,1H), 7.32 (s,5H), 7.50(d,J=8.3Hz,1H), 7.79(dd,J= 1.3Hz,8.3Hz,1H), 8.04(s,1H), 8.24(d,J=5.7Hz,1H)

Example 49

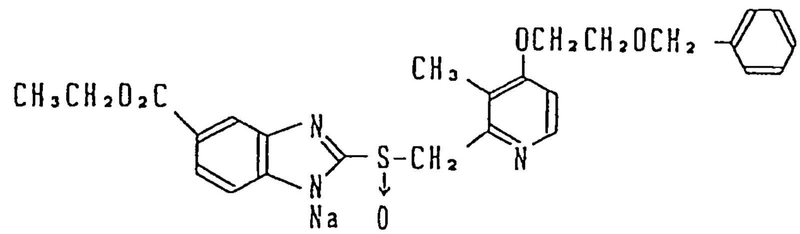
5-Ethoxycarbonyl-2-[{4-(2-benzyloxy)ethoxy-3-methylpyridine-2-yl}methylthio]-1H-benzimidazole



A mixture comprising 1.0 g of 5-carboxy-2-[{4-(2-benzyloxy)ethoxy-3-methylpyridine-2-yl}methylthio]-1H-benzimidazole, 200 ml of ethanol and 1 ml of concentrated sulfuric acid was heated under reflux for 4 hours, while dehydrating the system with a molecular sieve. The resulting mixture was neutralized with a saturated aqueous solution of sodium carbonate and distilled to remove the ethanol, followed by the addition of a saturated aqueous solution of sodium hydrogencarbonate. The obtained mixture was extracted with chloroform. The extract was dried over magnesium sulfate and filtered. The filtrate was concentrated to obtain a crude product. This crude product was purified by silica gel column chromatography to obtain 0.76 g of the title compound.
^{1}H-NMR(DMSO-d_6) δ ; 1.35(t,J=7.0Hz,3H), 2.25(s,3H), 3.7 ~3.9(m,2H), 4.15 ~4.3 (m,2H), 4.24-(q,J=7.0Hz,2H), 4.57(s,2H), 4.75(s,2H), 6.96(d,J=5.7Hz), 7.32(s,5H), 7.52(d,J=8.5Hz,1H), 7.79-(dd,J=1.3Hz,8.5 Hz,1H), 8.05(d,J=1.3Hz,1H), 8.24(d,J=5.7 Hz,1H)

Example 50

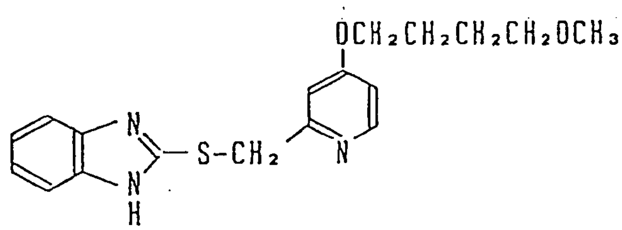
Sodium salt of 5-ethoxycarbonyl-2[{4-(2-benzyloxy)ethoxy-3-methylpyridine-2-yl}methylsulfinyl]-1H-benzimidazole



0.7 g of 5-ethoxycarbonyl-2-[{4-(2-benzyloxy)-ethoxy-3-methylpyridine-2-yl}methylthio]-1H-benzimidazole was dissolved in 50 ml of dichloromethane to obtain a solution. 0.3 g of 85% m-chloroperbenzoic acid was added to this solution at -45 °C. After 2 hours, the obtained mixture was heated to -30 °C, followed by the addition of 0.43 g of triethylamine. After 30 minutes, the obtained mixture was heated to -10 °C, followed by the addition of 50 ml of a saturated aqueous solution of sodium hydrogencarbonate. The obtained mixture was vigorously stirred at a room temperature for 30 minutes and extracted with dichloromethane. The extract was dried over magnesium sulfate and filtered. The filtrate was concentrated and the obtained residue was dissolved in 10 ml of dichloromethane, followed by the addition of 0.056 g of 60% sodium hydride. The obtained mixture was stirred at a room temperature for 30 minutes and distilled to remove the dichloromethane. The obtained residue was crystallized from ether to obtain 0.59 g of the title compound.
^{1}H-NMR(DMSO-d$_6$) δ ; 1.34(t,J = 7.0Hz,3H), 2.18(s,3H), 3.7 ~3.9(m,2H), 4.1~4.3 (m,2H), 4.24(q,J = 7 0Hz,2H), 4.57(s,3H), 4.65(s,2H), 6.94(d,J = 5.7Hz,1H), 7.30(s, 5H), 7.50 ~7.86(m,3H), 8.26(d,J = 5.7Hz, 1H)

Example 51

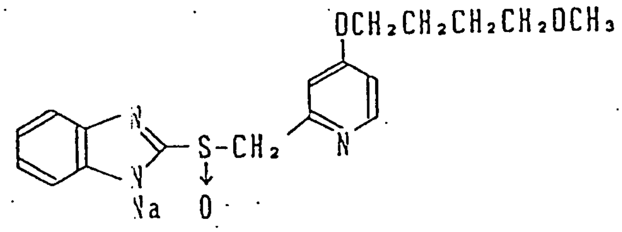
2-[4-(4-Methoxybutoxy)pyridine-2-yl]methylthio-1H-benzimidazole



A mixture comprising 2.55 g (0.017 mol) of 2-mercaptobenzimidazole, 5.09 g (0.022 mol) of 2-chloromethyl-4-(4-methoxybutoxy)pyridine, 0.84 g (0.020 mol) of 95% sodium hydroxide and 60 ml of ethanol was stirred at 40 °C for 1.5 hours. After the completion of the reaction, the reaction mixture was distilled to remove the solvent. The obtained residue was purified by silica gel column chromatography (ethyl acetate/n-hexane) to obtain 4.13 g of the title compound.
^{1}H-NMR(DMSO-d$_6$) δ ; 1.43~1.84(m,4H), 3.21 (s,3H), 3.31(t,J = 6.2Hz,2H), 3.99(t,J = 6.2Hz,2H), 4.59(s,2H), 6.75 ~6.89(m, 1H), 7.04 ~7.21(m,2H), 7.25~7.56(m, 2H), 8.31(d,J = 6.2Hz,1H)

Example 52

Sodium salt of 2-[4-(4-methoxybutoxy)pyridine-2-yl]methylsulfinyl-1H-benzimidazole

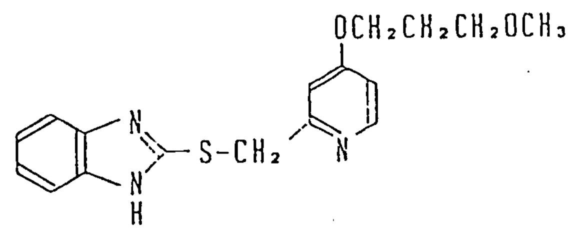


2.06 g (0.006 mol) of 2-[4-(4-methoxybutoxy)pyridine-2-yl]methylthio-1H-benzimidazole was dissolved in 80 ml of dichloromethane to obtain a solution. 1.30 g (0.006 mol) of 80% m-chloroperbenzoic acid and 5 ml of methanol were added to the solution at -40 °C in a nitrogen atmosphere. The obtained mixture was stirred for 1.5 hours. After the completion of the reaction, 1.0 g of triethylamine was added to the reaction mixture. The obtained mixture was heated to -10 °C, followed by the addition of 50 ml of a 2N aqueous solution of sodium carbonate. The obtained mixture was stirred at a room temperature for 30 minutes and extracted with 150 ml of dichloromethane twice. The extract was dried over magnesium sulfate and filtered. The filtrate was distilled to remove the solvent and the obtained residue was dried in a vacuum to obtain an oil. This oil was dissolved in 54 ml of 0.1N aqueous sodium hydroxide, followed by the addition of ethanol. The obtained mixture was distilled to remove the solvent. The obtained residue was washed with ether thrice and dried in a vacuum to obtain 2.02 g of the title compound as a white powder.

^{1}H-NMR(DMSO-d_6) δ ; 1.40~1.74(m,4H), 3.17 ~3.40(m,2H), 3.23(s,3H), 3.66~3.88(m, 2H), 4.48-(ABq,J=12.5Hz, $\Delta\nu$=12.7Hz,2H), 6.60~7.00(m,3H), 7.35~7.58(m,2H), 8.32(d,J=6.2Hz,1H)

Example 53

2-[4-(3-Methoxypropoxy)pyridine-2-yl]methylthio-1H-benzimidazole

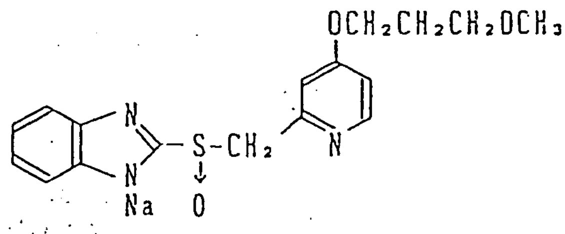


A mixture comprising 1.50 g (0.01 mol) of 2-mercapto-1H-benzimidazole, 3.20 g (0.015 mol) of 2-chloromethyl-4-(3-methoxypropoxy)pyridine, 0.51 g (0.012 mol) of 95% sodium hydroxide and 60 ml of ethanol was stirred at 40 °C for 0.5 hour and filtered. The filtrate was concentrated under a reduced pressure and purified by silica gel column chromatography (ethyl acetate/n-hexane) to obtain 3.27 g of the title compound as a colorless crystal.

^{1}H-NMR(DMSO-d_6) δ ; 1.62~2.06(m,2H), 3.16 (s,3H), 3.34(t,J=6.2Hz,2H), 3.97(t,J=6.2 Hz,2H), 4.51(s,2H), 6.62~6.84(m,1H), 6.88~7.16(m,2H), 7.20~7.48(m,2H), 8.20(d,J=6.2Hz,1H)

Example 54

Sodium salt of 2-[4-(3-methoxypropoxy)pyridine-2-yl]methylsulfinyl-1H-benzimidazole

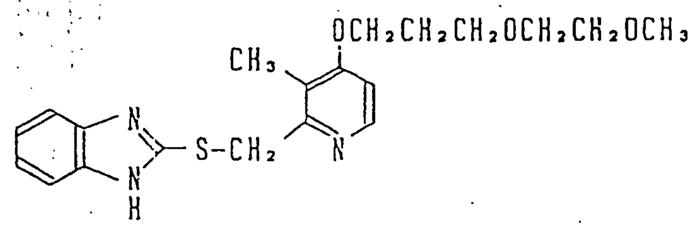


1.65 g (0.005 mol) of 2-[4-(3-methoxypropoxy)pyridine-2-yl]methylthio-1H-benzimidazole was dissolved in 50 ml of dichloromethane to obtain a solution. 1.08 g (0.005 mol) of 80% m-chloroperbenzoic acid was added to the solution at -40 °C in a nitrogen atmosphere. The obtained mixture was stirred for 15 minutes. After the completion of the reaction, 0.8 g of triethylamine was added to the reaction mixture. The obtained mixture was heated to -10 °C, followed by the addition of 30 ml of a 2N aqueous solution of sodium carbonate. The obtained mixture was stirred at a room temperature for 30 minutes and extracted with 100 ml of dichloromethane thrice. The extract was dried over magnesium sulfate and filtered. The filtrate was concentrated under a reduced pressure and dried in a vacuum. The obtained residue was dissolved in 50 ml of 0.1N aqueous sodium hydroxide, followed by the addition of ethanol. The obtained mixture was distilled to remove the solvent and the residue was washed with ether and dried in a vacuum to obtain 1.70 g of the title compound as a white crystal.

^{1}H-NMR(CMSO-d_6) δ ; 1.70~1.98(m,2H), 3.22 (s,3H), 3.37(t,J=6.2Hz,2H), 3.44~3.89 (m,2H), 4.47-(ABq,J=12.3Hz, $\Delta\nu$=10.6Hz, 2H), 6.70 ~6.94(m,4H), 7.42~7.53(m, 2H), 8.32(d,J=5.8Hz,1H)

Example 55

2-[4-{3-(2-Methoxyethoxy)propoxy}-3-methylpyridine-2-yl]methylthio-1H-benzimidazole

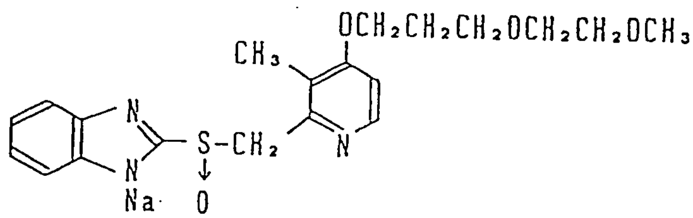


2.24 g of triethylamine and 1.27 g of methanesulfonyl chloride were added to a solution of 1.4 g of crude 2-hydroxymethyl-4-{3-(2-methoxy)}-3-methylpyridine in dichloromethane at -30 °C. The obtained mixture was gradually returned to a room temperature, followed by the addition of a saturated aqueous solution of sodium hydrogencarbonate. The obtained mixture was stirred for 30 minutes and extracted with chloroform. The extract was dried over magnesium sulfate and distilled under a reduced pressure to remove the chloroform. 1.9 g of crude [4-{3-(2-methoxyethoxy)propoxy}-3-methylpyridine-2-yl]methyl methanesulfonate was obtained as a red oil. 0.83 g of 2-mercapto-1H-benzimidazole was added to this oil. The obtained mixture was stirred together with 20 ml of ethanol at a room temperature for 30 minutes, followed by the addition of a saturated aqueous solution of sodium hydrogencarbonate. The obtained mixture was stirred at a room temperature for 30 minutes and extracted with chloroform. The extract was dried over magnesium sulfate and distilled under a reduced pressure to obtain a residue. This residue was chromatographed over a silica gel column and eluted with ethyl acetate/n-hexane to obtain 1.55 g of an oil.

^{1}H-NMR($CDCl_3$) δ ; 2.12(q,J=6.15Hz,2H), 2.25 (s,2H), 3.36(s,3H), 3.56(m,2H), 3.66(t, J=6.15Hz,2H), 4.14-(t,J=6.15Hz,2H), 4.37 (s,2H), 6.77(d,J=5.72Hz,1H), 7.1~7.25 (m,2H), 7.528(m,2H), 8.33(d,J=5.72Hz, 1H)

Example 56

Sodium salt of 2-[4-{3-(2-methoxyethoxy)propoxy}-3-methylpyridine-2-yl]methylsulfinyl-1H-benzimidazole

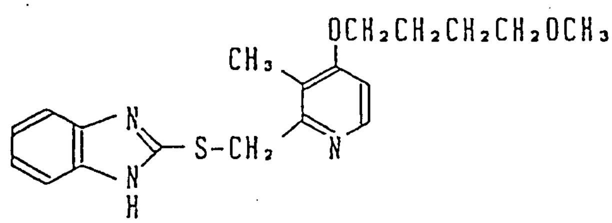


681 mg of 35% m-chloroperbenzoic acid was added in portions to a solution of 1.3 g of 2-[4-{3-(2-methoxyethoxy)propoxy}-3-methylpyridine-2-yl]methyl thio-1H-benzimidazole in 70 ml of dichloromethane under stirring and dehumidifying. The obtained mixture was stirred for 30 minutes, followed by the addition of 483 mg of triethylamine. The obtained mixture was heated to -20 °C, followed by the addition of a 2N aqueous solution of sodium carbonate. The obtained mixture was stirred at a room temperature for 30 minutes and extracted with dichloromethane twice. The extract was washed with a saturated aqueous solution of sodium hydrogencarbonate, dried over magnesium sulfate and distilled under a reduced pressure to obtain a crude oil. 30 ml of 0.1N aqueous sodium hydroxide and ethanol were added to this oil. The obtained mixture gas distilled under a reduced pressure at 40 °C to remove the medium. Ethanol was again added to the obtained residue and the obtained mixture was distilled under a reduced pressure to remove the medium. The obtained residue was crystallized from anhydrous ether to obtain 1.24 g of a crystal.

^{1}H-NMR(DMSO-d_6) δ ; 1.98(q,J=6.15Hz,2H), 2.15(s,3H), 3.22(s,3H), 3.47(m,4H), 3.56(t,J=6.15Hz,2H), 4.09-(t,J=6.15Hz, 2H), 4.542(ABq,J=13.18Hz, $\Delta\nu$=14.74Hz, 1H), 6.8~7.0(m,3H), 7.39 ~7.57(m,2H), 8.27-(d,J=5.71Hz,1H)

Example 57

2-[{4-(4-Methoxybutoxy)-3-methylpyridine-2-yl}methylthio]-1H-benzimidazole



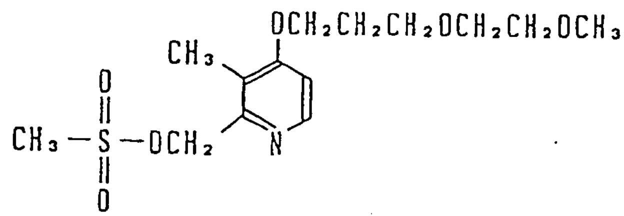
611 mg of triethylamine and 686 mg of methanesulfonyl chloride were added to a solution of 0.84 g of crude 2-hydroxy-4-(4-methoxybutoxy)-3-methylpyridine in 30 ml of dichloromethane at -20 °C under stirring and dehumidifying to obtain a mixture. This mixture was gradually brought to a room temperature, followed by the addition of a saturated aqueous solution of sodium hydrogencarbonate The obtained mixture was stirred for 30 minutes and extracted with chloroform. The extract was dried over magnesium sulfate and distilled under a reduced pressure to remove the chloroform. Thus, a red oil was obtained. 560 mg of 2-mercapto-1H-benzimidazole and 30 ml of ethanol were added to this oil. The obtained mixture was stirred at a room temperature for 30 minutes, made basic with a 2N aqueous solution of sodium carbonate and extracted with chloroform. The extract was dried over magnesium sulfate and distilled under a reduced pressure to remove the chloroform. The obtained residue was chromatographed over a silica gel column and eluted with ethyl acetate/n-hexane to obtain 0.42 g of an oil.

^{1}H-NMR($CDCl_3$) δ ; 1.4 ~2.16(m,4H), 2.26(s, 3H), 3.35(s,3H), 3.45(t,J=5.72Hz,2H), 4.06(t,J=5.72Hz,2H),

4.37(s,2H), 6.74 (d,J = 5.71 Hz,1H), 7.1~7.25(m,2H), 7.48 ~7.56(m,2H), 8.33(d,J = 5.72Hz,1H)

Preparative Example 15

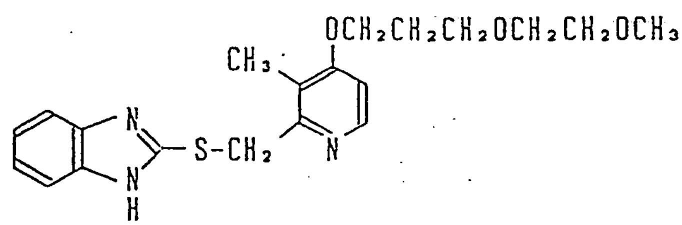
[4-{3-(2-Methoxyethoxy)propoxy}-3-methylpyridine-2-yl]methyl methanesulfonate



2.24 g of triethylamine and 1.27 g of methanesulfonyl chloride were added to a solution of 1.4 g of crude 2-hydroxy-4-{3-(2-methoxyethoxy)}-3-methylpyridine in dichloromethane at -30 °C to obtain a mixture. This mixture was brought to a room temperature, followed by the addition of a saturated aqueous solution of sodium hydrogencarbonate. The obtained mixture was stirred for 30 minutes and extracted with chloroform. The extract was dried over magnesium sulfate and distilled under a reduced pressure to remove the chloroform. 1.9 g of a crude red oil was obtained.

Example 58

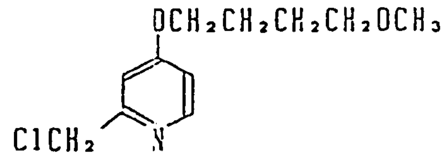
2-[4-{3-(2-Methoxyethoxy)propoxy}-3-methylpyridine-2-yl]methylthio-1H-benzimidazole



A mixture comprising 1.9 g of crude [4-{3-(2-methoxyethoxy)propoxy}-3-methylpyridine-2-yl]methyl methanesulfonate, 0.83 g of 2-mercapto-1H-benzimidazole and 20 ml of ethanol was stirred at a room temperature for one hour, made basic with a saturated aqueous solution of sodium hydrogencarbonate and extracted with chloroform. The extract was dried over magnesium sulfate and distilled under a reduced pressure. The obtained residue was chromatographed over a silica gel column and eluted with ethyl acetate/n-hexane to obtain 1.5 g of an oily product.
^{1}H-NMR(CDCl$_3$) δ ; 2.12(q,J = 6.2Hz,2H), 2.25 (s,3H), 3.36(s,3H), 3.57(m,2H) 3.66(t, J = 6.2Hz,2H), 4.14-(t,J = 6.2Hz,2H), 4.37 (s,2H), 6.77(d,J = 3.1 Hz,1H), 7.15(m,2H), 7.53(m,2H), 8.39(d,J = 3 1Hz,1H)

Preparative Example 16

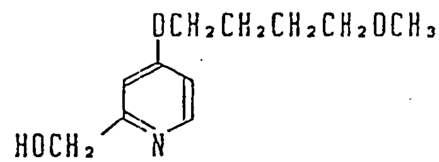
2-Chloromethyl-4-(4-methoxybutoxy)pyridine



5.6 g of crude 2-hydroxymethyl-4-(4-methoxybutoxy)-pyridine was dissolved in 80 ml of chloroform to obtain a solution. A solution of 3.8 g of thionyl chloride in 10 ml of chloroform was dropwise added to this solution at 0 °C. The obtained mixture was stirred at 0 °C for one hour. After the completion of the reaction, the reaction mixture was neutralized with a saturated aqueous solution of sodium hydrogencarbonate and extracted with 200 ml of chloroform twice. The extract was dried over magnesium sulfate and filtered. The filtrate was distilled to remove the solvent. The obtained residue was dried in a vacuum to obtain 5.09 g of the title compound as a crude oil.
^{1}H-NMR($CDCl_3$) δ ; 1.55~2.05(m,4H), 3.35(s, 3H), 3.38 ~3.53(m,2H), 3.91~4.17(m, 2H), 4.61(s,2H), 6.55 ~7.01(m,2H), 8.36(d,J=6.2Hz,1H)

Preparative Example 17

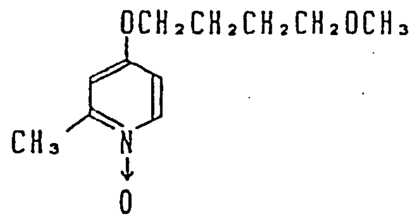
2-Hydroxymethyl-4-(4-methoxybutoxy)pyridine



5.06 g (0.024 mol) of 4-(4-methoxybutoxy)-2-methylpyridine 1-oxide was dissolved in 80 ml of acetic anhydride to obtain a solution. This solution was stirred at 100 °C for one hour, cooled and distilled to remove the solvent. 150 ml of 1N hydrochloric acid was added to the residue. The obtained mixture was stirred at 100 °C for one hour, cooled, neutralized with sodium hydrogencarbonate and extracted with 200 ml of chloroform twice. The extract was dried over magnesium sulfate and filtered. The filtrate was distilled to remove the solvent and the residue was dried in a vacuum to obtain 5.66 g of the title compound as a crude oil.
^{1}H-NMR($CDCl_3$) δ ; 1.58~2.08(m,4H), 3.32~3.54(m,2H), 3.34(s,3H), 3.82~4.16(m, 2H), 4.69(s,2H), 5.02(s,1H)-), 6.54~6.88 (m,2H), 8.30(d,J=6.2Hz,1H)

Preparative Example 18

4-(4-Methoxybutoxy)-2-methylpyridine 1-oxide



6.77 g (0.065 mol) of 4-methoxybutanol was dissolved in 60 ml of dimethyl sulfoxide to obtain a solution. 2.6 g (0.065 mol) of 60% sodium hydride was added to this solution at a room temperature in a nitrogen atmosphere. The obtained mixture was heated to 60 °C, stirred for one hour and cooled to a room temperature. A solution of 4.66 g (0.032 mol) of 4-chloro-2-methylpyridine 1-oxide in 20 ml of dimethyl sulfoxide was dropwise added to the resulting mixture. The obtained mixture was stirred at 40 °C for one hour. After the completion of the reaction, 5 ml of water was added to the mixture and the obtained mixture was evaporated to dryness to remove the solvent. 150 ml of water was added to the residue. The obtained mixture was extracted with 200 ml of chloroform four times. The extract was dried over magnesium sulfate and filtered. The filtrate was distilled to remove the solvent. The residue was purified by silica gel column chromatography (ethyl acetate/methanol) to obtain 5.06 g of the title compound as an oil.
^{1}H-NMR(CDCl$_3$) δ ; 1.54~2.07(m,4H), 2.52(s, 3H), 3.36(s,3H), 3.44(t,J=6.2Hz,2H), 4.01(t,J=6.2Hz,2H), 6.60~6.84(m,2H), 8.14(d,J=5.3Hz,1H)

Preparative Example 19

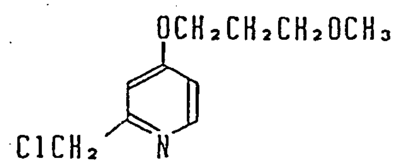
4-Methoxybutanol

$CH_3OCH_2CH_2CH_2CH_2OH$

27.04 g (0.3 mol) of 1,4-butanediol was dissolved in 150 ml of tetrahydrofuran to obtain a solution. 7.2 g (0.18 mol) of 60% sodium hydride was added to this solution at 0 °C in a nitrogen atmosphere. The obtained mixture was heated under reflux for one hour and cooled to 0 °C 21.73 g (0.15 mol) of 98% methyl iodide was dropwise added to the resulting mixture. The obtained mixture was stirred at a temperature of 30 °C or below for 1.5 hours. After the completion of the reaction, the reaction mixture was filtered. The filtrate was distilled to remove the solvent. 200 ml of water was added to the residue and the obtained mixture was washed with 200 ml of n-hexane and extracted with 200 ml of chloroform four times. The extract was dried over magnesium sulfate and filtered. The filtrate was distilled to remove the solvent. 14.5 g of the title compound was obtained.
^{1}H-NMR(CDCl$_3$) δ ; 1.54~1.80(m,4H), 1.71(s, 1H), 3.32(s,3H), 3.34 ~3.73(m,4H)

Preparative Example 20

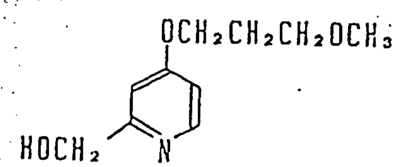
2-Chloromethyl-4-(3-methoxypropoxy)pyridine



A solution of 2.60 g (0.022 mol) of thionyl chloride in 10 ml of chloroform was dropwise added to a solution of 3.64 g (0.018 mol) of 2-hydroxymethyl-4-methoxypropoxypyridine in 60 ml of chloroform under cooling with ice. The obtained mixture was stirred for one hour, neutralized with a saturated aqueous solution of sodium hydrogencarbonate and extracted with chloroform. The chloroform layer was dried over magnesium sulfate and filtered. The filtrate was concentrated under a reduced pressure to obtain 3.23 g of the title compound as a crude product.
^{1}H-NMR($CDCl_3$) δ ; 1.80~2.20(m,2H), 3.31(s, 3H), 3.49((t,J=6.2Hz,2H), 4.07(t,J=6.2 Hz,2H), 4.55(s,2H), 6.52~6.96(m,2H), 8.26(d,J=5.3Hz,1H)

Preparative Example 21

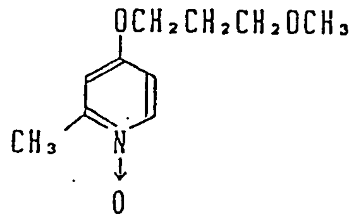
2-Hydroxymethyl-4-(3-methoxypropoxy)pyridine



4.05 g (0.02 mol) of 4-methoxypropoxy-2-methylpyridine 1-oxide was dissolved in 50 ml of acetic anhydride to obtain a solution. This solution was stirred at 90°C for 0.5 hour and cooled, followed by the addition of ethanol. The obtained mixture was concentrated under a reduced pressure, followed by the addition of 150 ml of 1N hydrochloric acid. The obtained mixture was stirred at 100°C for one hour, cooled, neutralized with sodium hydrogencarbonate and extracted with chloroform. The extract was dried over magnesium sulfate and filtered. The filtrate was distilled to remove the solvent. Thus, 3.64 g of the title compound was obtained as a crude product.
^{1}H-NMR($CDCl_3$) δ ; 1.83~2.20(m,2H), 3.30(s, 3H), 3.49((t,J=5.3Hz,2H), 4.05(t,J=5.3 Hz,2H), 4.64(s,2H), 4.70(s,1H), 6.48~ 6.86(m,2H), 8.21(d,J=6.2Hz,1H)

Preparative Example 22

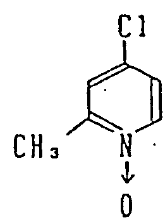
4-(3-Methoxypropoxy)-2-methylpyridine 1-oxide



5.85 g (0.065 mol) of methoxypropanol was dissolved in 60 ml of dimethyl sulfoxide to obtain a solution. 2.6 g (0.065 mol) of sodium hydride was added to this solution at a room temperature in a nitrogen atmosphere. The obtained mixture was stirred at 60 °C for 0.5 hour. A solution of 4.66 g (0.0325 mol) of 4-chloro-2-methylpyridine 1-oxide in 20 ml of dimethyl sulfoxide was dropwise added to the mixture under cooling with ice. The mixture was stirred at 40 °C for one hour. After the completion of the reaction, the reaction mixture was concentrated under a reduced pressure to obtain a solid. 200 ml of water was added to this solid. The obtained mixture was extracted with chloroform and the obtained extract was dried over magnesium sulfate and filtered. The filtrate was concentrated under a reduced pressure and purified by silica gel column chromatography (ethyl acetate/methanol) to obtain 4.09 g of the title compound.
^{1}H-NMR($CDCl_3$) δ ; 1.80~2.24(m,2H), 2.48(s, 3H), 3.31(s,3H), 3.48(t,J=6.3Hz,2H), 4.02(t,J=6.3Hz,2H), 6.50~6.78(m,2H), 8.04(d,J=7.2Hz,1H)

Preparative Example 23

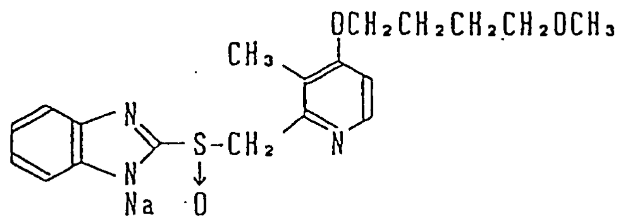
4-Chloro-2-methylpyridine 1-oxide



15.4 g (0.1 mol) of 2-methyl-4-nitropyridine 1-oxide was added to 78.5 g (1 mol) of acetyl chloride at -10 °C. The obtained mixture was stirred under cooling with ice for 0.5 hour. After the completion of the reaction, 300 ml of ice-water was added to the reaction mixture. The obtained mixture was neutralized with sodium carbonate and extracted with chloroform. The extract was dried over magnesium sulfate and filtered. The filtrate was concentrated under a reduced pressure and purified by silica gel column chromatography (ethyl acetate/n-hexane/methanol) to obtain 4.7 g of the title compound.
^{1}H-NMR($CDCl_3$) δ ; 2.48(s,3H), 6.94~7.30(m, 2H), 8.09(d,J=7.2Hz,1H)

Example 59

Sodium salt of 2-[{4-(4-methoxybutoxy)-3-methylpyridine-2-yl}methylsulfinyl]-1H-benzimidazole

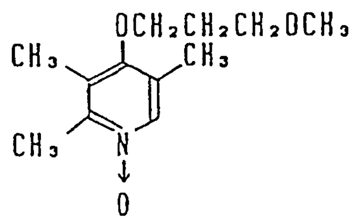


0.4 g of 2-[{4-(4-methoxybutoxy)-3-methylpyridine-2-yl}methylthio]-1H-benzimidazole was dissolved in 40 ml of dichloromethane under dehumidifying to obtain a solution. 227 mg of m-chloroperbenzoic acid was added in portions to this solution at -40 °C The obtained mixture was stirred for 30 minutes, followed by the addition of 160 mg of triethylamine. The obtained mixture was heated to -20 °C, followed by the addition of 30 ml of a 2N aqueous solution of sodium carbonate. The obtained mixture was stirred for 40 minutes and extracted with dichloromethane. The extract was washed with a saturated aqueous solution of sodium hydrogencarbonate, dried over magnesium sulfate and distilled under a reduced pressure to remove the dichloromethane. Thus, 0.43 g of an oily product was obtained. This product was dissolved in a mixture comprising 11.2 ml of 0.1N aqueous sodium hydroxide and 30 ml of ethanol and the obtained solution was distilled under a reduced pressure to remove the solvent. Ethanol was added to the obtained residue and the obtained mixture was distilled under a reduced pressure to remove the solvent. The residue was crystallized from ethanol/ether to obtain 0.37 g of the title compound as a crystal.

^{1}H-NMR(DMSO-d_6) δ ; 1.84(m,4H), 2.16(s,3H), 3.24(s,3H), 3.38(t,J = 6.2Hz,2H), 4.06(t, J = 6.2Hz,2H), 4.55-(ABq,J = 13.2Hz, $\Delta\nu$ = 18.1 Hz,2H), 6.8 ~6.98(m,3H), 7.4 ~7.6(m, 2H), 8.27(d,J = 5.3Hz,1H)

Preparative Example 24

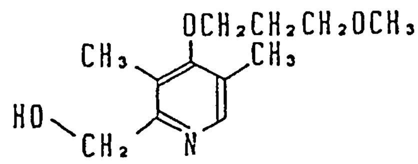
4-(3-Methoxypropoxy)-2,3,5-trimethylpyridine 1-oxide



4.5 g (0.05 mol) of methoxypropanol was dissolved in 45 ml of dimethyl sulfoxide to obtain a solution. 2.0 g of 60% sodium hydride was added to this solution at a room temperature in a nitrogen atmosphere. The obtained mixture was heated to 60 °C and stirred for one hour. After the completion of the reaction, a solution of 4.3 g (0.025 mol) of 4-chloro-2,3,5-trimethylpyridine 1-oxide in 15 ml of dimethyl sulfoxide was dropwise added to the reaction mixture at a room temperature. The obtained mixture was stirred at 60 °C for 5 hours, cooled and distilled to dryness to remove the solvent. 200 ml of water was added to the obtained residue. The obtained mixture was extracted with 150 ml of chloroform five times. The extract was dried over magnesium sulfate and filtered. The filtrate was distilled to remove the solvent. The residue was purified by silica gel column chromatography (ethyl acetate/n-hexane) to obtain 4.27 g of the title compound as an oil.

Preparative Example 25

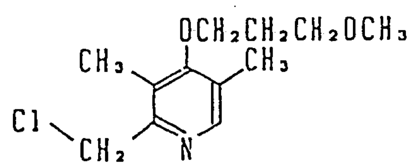
2-Hydroxymethyl-4-(3-methoxypropoxy)-3,4-dimethylpyridine



4.25 g (0.019 mol) of 4-(3-methoxypropoxy)-2,3,5-trimethylpyridine 1-oxide was dissolved in 40 ml of acetic anhydride to obtain a solution. This solution was stirred at 100 °C for 30 minutes, cooled and distilled to remove the solvent. Thus, an oil was obtained. 50 ml of 1N hydrochloric acid was added to the oil. The obtained mixture was stirred at 100 °C for one hour, cooled, neutralized with sodium hydrogencarbonate and extracted with 150 ml of chloroform thrice. The extract was dried over magnesium sulfate and filtered. The filtrate was distilled to remove the solvent. The obtained residue was dried in a vacuum to obtain 4.70 g of the title compound as a crude oil.
^{1}H-NMR(CDCl$_3$) δ ; 1.80~2.28(m,2H), 2.08(s, 3H), 2.23(s,3H), 3.34(s,3H), 3.58(t,J = 6.2Hz,2H), 3.87-(t,J = 6.2Hz,2H), 4.57(s, 2H), 8.10(s, 1H)

Preparative Example 26

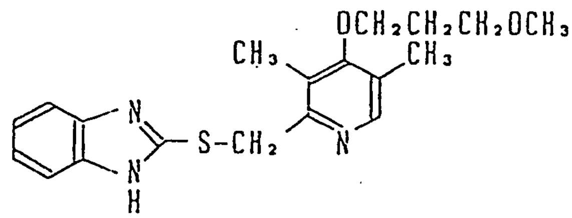
2-Chloromethyl-4-(3-methoxypropoxy)-3,5-dimethylpyridine



4.70 g of crude 2-hydroxymethyl-4-(3-methoxypropoxy)-3,5-dimethylpyridine was dissolved in 50 ml of chloroform to obtain a solution. A solution of 2.7 g of thionyl chloride in 10 ml of chlorloform was dropwise added to the above solution at 0 °C and the obtained mixture was stirred at 0 °C for one hour. After the completion of the reaction, the reaction mixture was neutralized with a saturated aqueous solution of sodium hydrogencarbonate and extracted with 150 ml of chloroform twice. The extract was dried over magnesium sulfate and filtered. The filtrate was distilled to remove the solvent. The obtained residue was dried in a vacuum to obtain 4.52 g of the title compound as a crude oil.
^{1}H-NMR(CDCl$_3$) δ ; 1.70~2.20(m,2H), 2.26(s, 3H), 2.34(s,3H), 3.38(s,3H), 3.61(t,J = 6.2Hz,2H), 3.91-(t,J = 6.2Hz,2H), 4.67(s, 2H), 8.18(s,1H)

Example 60

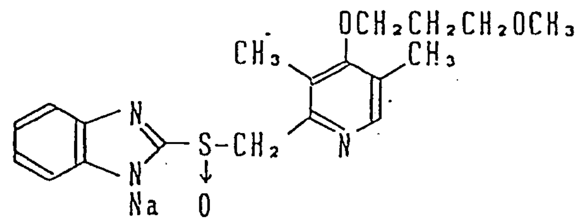
2-[4-(3-Methoxypropoxy)-3,4-dimethylpyridine-2-yl]methylthio-1H-benzimidazole



A mixture comprising 2.25 g (0.015 mol) of 2-mercaptobenzimidazole, 4.52 g (0.0185 mol) of 2-chloromethyl-4-(3-methoxypropoxy)-3,5-dimethylpyridine, 0.63 g (0.015 mol) of 95% sodium hydroxide and 50 ml of ethanol was stirred at 40°C for 6 hours. After the completion of the reaction, the reaction mixture was distilled to remove the solvent. The residue was purified by silica gel column chromatography (ethyl acetate/n-hexane) to obtain 4.62 g of the title compound as a pale yellow oil.

Example 61

Sodium salt of 2-[4-(3-methoxypropoxy)-3,4-dimethylpyridine-2-yl]methylsulfinyl-1H-benzimidazole

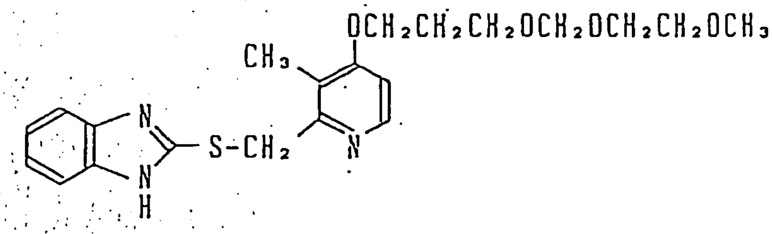


1.5 g of 2-[4-(3-methoxypropoxy)-3,4-dimethylpyridine-2-yl]methylthio-1H-benzimidazole was dissolved in 80 ml of dichloromethane under dehumidifying to obtain a solution. 870 mg of m-chloroperbenzoic acid was added to the solution in portions at -40°C. The obtained mixture was stirred for 30 minutes, followed by the addition of 599 mg of triethylamine. The obtained mixture was heated to -20°C, followed by the addition of 80 ml of a 2N aqueous solution of sodium carbonate. The obtained mixture was stirred for one hour and extracted with dichloromethane. The extract was washed with a saturated aqueous solution of sodium hydrogencarbonate, dried over magnesium sulfate and distilled under a reduced pressure to obtain 1.4 g of a crystal. 800 mg of the crystal was dissolved in a mixture comprising 21.4 ml of 0.1N aqueous sodium hydroxide and ethanol. The obtained solution was distilled under a reduced pressure to remove the solvent. The obtained residue was dissolved in ethanol and the solution was distilled under a reduced pressure to remove the solvent. The obtained residue was crystallized from ethanol/ether to obtain 800 mg of a crystal.

^{1}H-NMR(DMSO-d_6) δ ; 1.94(qui,J=6.2Hz,2H), 2.17(s,3H), 2.19(s,3H), 3.25(s,3H), 3.51 (t,J=6.6Hz,2H), 3.80-(t,J=6.6Hz,2H), 4.51 (ABq,J=13.2Hz, $\Delta\nu$=17.0Hz), 6.8~6.9 (m,2H), 7.4, ~7.7(m,2H), 8.21(s,1H)

Example 62

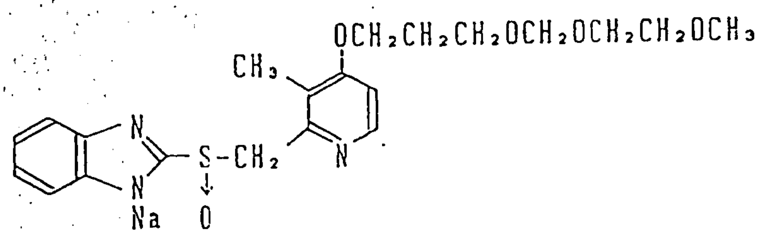
2-[4-[3-{(2-Methoxyethoxy)methoxy}propoxy]-3-methylpyridine-2-yl]methylthio-1H-benzimidazole



1.8 g of 2-hydroxymethyl-4-[3-{(2-methoxyethoxy)methoxy}propoxy]-3-methylpridine was dissolved in 40 ml of dichloromethane under dehumidifying to obtain a solution, followed by the addition of 2.47 g of triethylamine. 1.4 g of methanesulfonyl chloride was added to the obtained mixture in portions under cooling with ice. The obtained mixture was stirred for 30 minutes, made basic with a saturated aqueous solution of carbonic acid and extracted with chloroform. The extract was dried over magnesium sulfate and distilled under a reduced pressure. The residue was dissolved in 30 ml of ethanol, followed by the addition of 917 mg of 2-mercapto-1H-benzimidazole and 367 mg of sodium hydroxide. The obtained mixture was stirred at a room temperature for 30 minutes and distilled under a reduced pressure to remove the ethanol. The obtained residue was chromatographed over a silica gel column and eluted with ethyl acetate/n-hexane to obtain 2.1 g of the title thio ether compound.
^{1}H-NMR($CDCl_3$) δ ; 2.11(qui,J=6.2Hz,2H), 2.25(s,3H), 3.35(s,3H), 3.58(m,4H), 3.75(t,J=6.2Hz,2H), 4.13-(t,J=6.2Hz,2H), 4.38(s,2H), 4.71(s,2H), 6.75(d,J=5.7Hz, 1H), 7.1~7.3(m,2H), 7.4~7.6(m,2H), 8.32-(d,J=5.7Hz,1H)

Example 63

Sodium salt of 2-[4-[3-{(2-methoxyethoxy)methoxy}propoxy]-3-methylpyridine-2-yl]methylsulfinyl-1H-benzimidazole

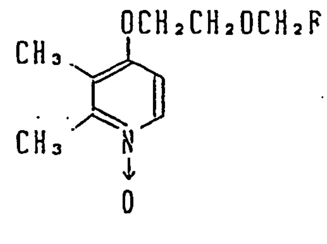


1.1 g of 2-[4-[3-{(2-methoxyethoxy)methoxy}propoxy]-3-methylpyridine-2-yl]methylthio-1H-benzimidazole was dissolved in 80 ml of dichloromethane under dehumidifying to obtain a solution. 544 mg of m-chloroperbenzoic acid was added to this solution in portions at -40 °C. The obtained mixture was stirred for 30 minutes, followed by the addition of 379 mg of triethylamine. The obtained mixture was heated to -20 °C, followed by the addition of 40 ml of a 2N aqueous solution of sodium carbonate. The obtained mixture was stirred fro 30 minutes and extracted with chloroform. The extract was washed with a saturated aqueous solution of sodium hydrogencarbonate, dried over magnesium sulfate and distilled under a reduced pressure to remove the solvent. The obtained residue was dissolved in a mixture comprising 24 ml of 0.1N aqueous sodium hydroxide and 40 ml of ethanol. The obtained solution was distilled under a reduced pressure to remove the solvent, followed by the addition of 40 ml of ethanol. The obtained mixture was again distilled under a reduced pressure to remove the ethanol. The residue was crystallized from ethanol/ether to obtain 0.98 g of the title compound.
^{1}H-NMR(DMSO-d_6) δ ; 2.02(qui,J=6.2Hz,2H), 2.17(s,3H), 3.23(s,3H), 3.49(m.4H), 3.65 (t,J=6.2Hz,2H), 4.12-

(t,J = 6.2Hz,2H), 4.56 (ABq,J = 21.1Hx, Δ ν = 16.8Hz,2H), 4.62(s, 2H), 6.84 ~6.99(m,3H), 7.4 ~7.5(m,2H), 8.28-(d,J = 5.7Hz,1H)

Preparative Example 27

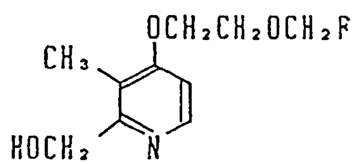
4-(2-Fluoromethoxy)ethoxy-2,3-dimethylpyridine N-oxide



0.49 g of sodium hydride was gradually added to a solution of 1.0 g of 4-(2-hydroxyethoxy)-2,3-dimethylpyridine N-oxide in 40 ml of dimethylformamide in a nitrogen atmosphere at a room temperature. After the stopping of foaming, 1 ml of bromofluoromethane was added to the obtained mixture at -50 °C. The resulting mixture was gradually heated and stirred at 15 to 20 °C for 3 hours. Ethanol was added to the resulting mixture to consume excess sodium hydride. 5 ml of 1N aqueous hydrochloric acid was added to the mixture and gaseous nitrogen was passed through the obtained mixture to expel excess bromofluoromethane. Water was added to the resulting mixture. The obtained mixture was extracted with chloroform and the extract was dried over magnesium sulfate and distilled under a reduced pressure to remove the solvent. The residue was chromatographed over a silica gel column and eluted with chloroform containing 1 to 5% of methanol to obtain 0.6 g of the title compound.
^{1}H-NMR($CDCl_3$) δ ; 2.24(s,3H), 2.56(s,3H), 4.24(m,5H), 5.3(d,J = 55.8Hz,2H), 6.54 (d,J = 6.2Hz,1H), 8.12-(d,J = 6.2Hz,1H)

Preparative Example 28

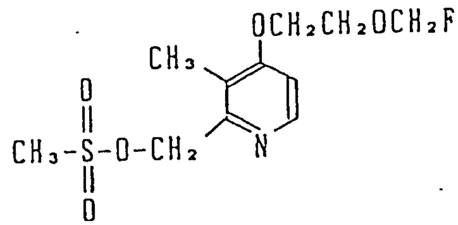
4-(2-Fluoromethoxy)ethoxy-2-hydroxymethyl-3-methylpyridine



A mixture comprising crude 4-(2-fluoromethoxy)-ethoxy-2,3-dimethylpyridine N-oxide prepared from 6.0 g of crude 4-(2-hydroxyethoxy)-2,3-dimethylpyridine N-oxide and 40 ml of acetic anhydride was stirred under heating at 90 to 100 °C for 40 minutes and distilled under a reduced pressure to remove the acetic anhydride. The residue was made weakly basic with a 2N aqueous solution of sodium carbonate and extracted with chloroform. The extract was dried over magnesium sulfate and distilled under a reduced pressure to remove the solvent. The obtained residue was dissolved in 30 ml of ethanol, followed by the addition of 0.38 g of sodium hydroxide. The obtained mixture was stirred at a room temperature for 30 minutes, made weakly basic with a saturated aqueous solution of ammonium chloride and extracted with chloroform. The extract was dried over magnesium sulfate and distilled under a reduced pressure to remove the solvent. The residue was chromatographed over a silica gel column and eluted with ethyl acetate/n-hexane to obtain 1.2 g of the title compound as a crystal.
^{1}H-NMR ($CDCl_3$) δ ; 2.06(s,3H), 4.17(m,4H), 4.64(s,2H), 5.35(d,J = 56.3Hz,2H, 6.71 (d,J = 5.7Hz,1H), 8.30-(d,J = 5.7Hz,1H)

Preparative Example 29

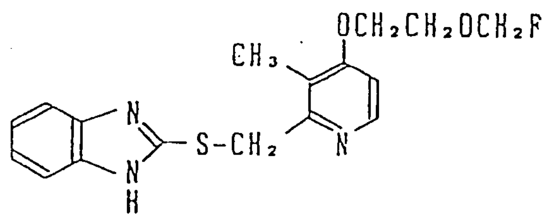
{4-(2-Fluoromethoxy)ethoxy-3-methylpyridine-2-yl}methyl methanesulfonate



160 mg of methanesulfonyl chloride was dropwise added to a solution of 0.2 g of 4-(2-fluoromethoxy)-ethoxy-2-hydroxymethyl-3-methyXpyridine and 143 mg of triethylamine in 10 ml of chloroform under dehumidifying at -50 °C. The obtained mixture was gradually heated to a room temperature, made basic with a saturated aqueous solution of sodium hydrogencarbonate and extracted with chloroform. The extract was dried over magnesium sulfate and distilled to remove the solvent. 0.38 g of the title compound was obtained as a crude oil.
^{1}H-NMR($CDCl_3$) δ ; 2.30(s,3H), 3.08(s,3H), 4.2(m,4H), 5.4(d,J = 55.8Hz,2H), 5.38(s, 2H), 6.84(d,J = 6Hz,1H), 8.36(d,J = 6Hz,1H)

Example 64

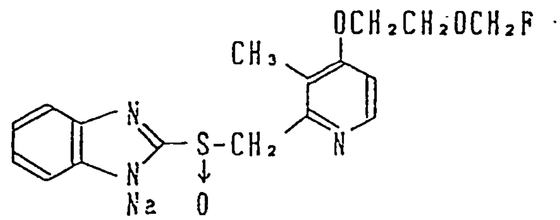
2-[{4-(2-Fluoromethoxy)ethoxy-3-methylpyridine-2-yl}methylthio]-1H-benzimidazole



A mixture comprising crude {4-(2-fluoromethoxy)ethoxy-3-methylpyridine-2-yl}methyl methanesulfonate prepared from 0.6 g of 4-(2-fluoromethoxy)ethoxy-2-hydroxymethyl-3-methylpyridine, 0.42 g of 2-mercapto-1H-benzimidazole and 30 ml of ethanol was stirred at a room temperature for 30 minutes and distilled under a reduced pressure to remove the ethanol. The obtained residue was chromatographed over a silica gel column and eluted with methanol/ethyl acetate to obtain 0.3 g of an oily product.
^{1}H-NMR($CDCl_3$) δ ; 2.25(s,3H), 2.98(s,3H), 4.13(m,4H), 4.41(s,2H), 5.33(d,J = 56.3 Hz,2H), 6.72-(d,J = 5.7Hz,1H), 7.1 ~7.2 (m,2H), 7.4 ~7.6(m,2H), 8.32(d,J = 5.7 Hz,1H)

Example 65

Sodium salt of 2-[{4-(2-fluoromethoxy)ethoxy-3-methylpyridine-2-yl}methylsulfinyl]-1H-benzimidazole

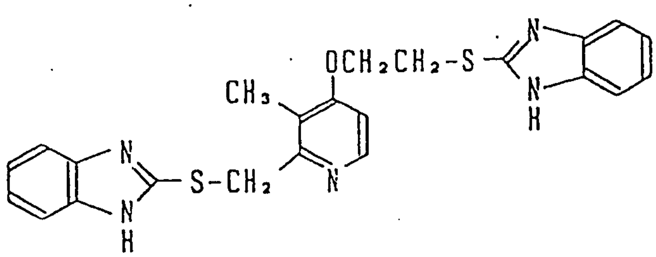


184 mg of m-chloroperbenzoic acid was added in portions to a solution of 0.3 g of 2-[{4-(2-fluoromethoxy)ethoxy-3-methylpyridine-2-yl}methylthio]-1H-benzimidazole in 30 ml of dichloromethane under stirring and dehumidifying at -40°C. The obtained mixture was stirred for 30 minutes, followed by the addition of 129 mg of triethylamine. The obtained mixture was brought to a room temperature, made weakly basic with a saturated aqueous solution of sodium hydrogencarbonate and extracted with chloroform. The extract was dried over magnesium sulfate and distilled under a reduced pressure to remove the solvent. The obtained residue was dissolved in 30 ml of anhydrous tetrahydrofuran in a nitrogen atmosphere to obtain a solution. 36.2 mg of 60% sodium hydride was added to this solution at -20°C. After the disappearance of foams, the obtained mixture was distilled under a reduced pressure to remove the tetrahydrofuran. The residue was crystallized from anhydrous ether to obtain 260 mg of the title compound as a crystal.

^{1}H-NMR(DMSO-d_6) δ ; 2.18(s,3H), 4.14(m,4H), 4.56(ABq,J=13.2Hz, Δ ν=21.3Hz,2H), 5.37 (d,J=56.7Hz,2H), 6.8~7.0(m,3H), 7.4~ 7.5(m,2H), 8.29(d,J=5.3Hz,1H)

Example 66

2-[[4-{2-(1H-Benzimidazol-2-ylthio)ethoxy}-3-methylpyridine-2-yl]methythio]-1H-benzimidazole

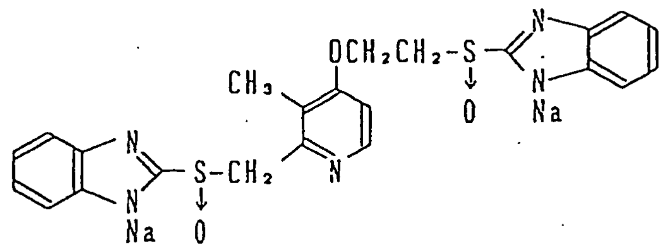


A mixture comprising 1.34 g (0.004 mol) of 2-[{4-(2-chloroethoxy)-3-methylpyridine-2-yl}methylthio]-1H-benzimidazol, 0.53 g (0.0035 mol) of 2-mercapto-1H-benzimidazole, 0.17 g (0.004 mol) of 95% sodium hydroxide and 30 ml of ethanol was stirred at 80°C for 8 hours. After the completion of the reaction, the reaction mixture was filtered to remove inorganic matter. The filtrate was distilled to remove the solvent. The residue was purified by silica gel column chromatography (ethyl acetate/n-hexane) to obtain 1.08 g of the title compound as a white crystal.

^{1}H-NMR(DMSO-d_6) δ ; 2.15(s,3H), 3.73(t,J= 7.1Hz,2H), 4.23(t,J=7.1Hz,2H), 4.68(s, 2H), 6.96 ~7.22(m,5H), 7.32~7.54(m, 4H), 8.25(d,J=5.3Hz, 1H)

Example 67

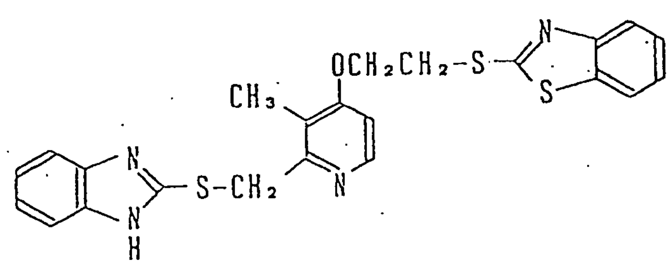
Disodium salt of 2-[[4-{2-(1H-benzimidazol-2-ylsulfinyl)ethoxy}-3-methylpyridine-2-yl]methylsulfinyl]-1H-benzimidazole



0.90 g (0.002 mol) of 2-[[4-{2-(1H-benzimidazol-2-ylthio)ethoxy}-3-methylpyridine-2-yl]methylthio]-1H benzimidazole was suspended in 40 ml of dichloromethane to obtain a suspension. Methanol was added to the suspension, until the suspension became transparent. 0.43 g (0.002 mol) of 80% m-chloroperbenzoic acid was added to the resulting mixture in a nitrogen atmosphere at -60°C. The obtained mixture was stirred for 0.5 hour. After the completion of the reaction, 0.5 g of triethylamine was added to the reaction mixture. The obtained mixture was heated to -10°C, followed by the addition of 30 ml of a saturated aqueous solution of sodium hydrogencarbonate. The obtained mixture was stirred at a room temperature for 0.5 hour and filtered. The filtrate was extracted with 100 ml of dichloromethane thrice. The extract was dried over magnesium sulfate and filtered. The filtrate was distilled to remove the solvent. 0.14 g of the obtained residue was dissolved in 0.1N aqueous sodium hydroxide, followed by the addition of ethanol. The obtained mixture was distilled to remove the solvent. The obtained residue was washed with ether to obtain 0.15 g of the title compound as a yellow crystal.
^{1}H-NMR(DMSO-d$_6$) δ ; 2.18(s,3H), 3.20~3.75 (m,2H), 4.19~4.74(m,4H), 6.68~7.08(m, 5H), 7.16 ~7.53(m,4H), 8.20(d,J=6.2Hz, 1H)

Example 68

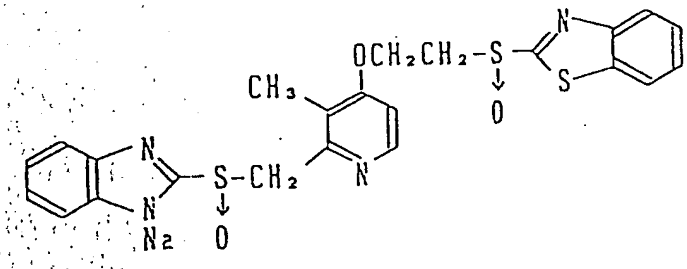
2-[[4-{2-(Benzothianol-2-ylthio)ethoxy}-3-methylpyridine-2-yl]methylthio]-1H-benzimidazole



A mixture comprising 1.34 g (0.004 mol) of 2-[{4-(2-chloroethoxy)-3-methylpyridine-2-yl}methylthio]-1H-benzimidazole, 0.59 g (0.0035 mol) of 2-mercaptobenzothiazole, 0.17 g (0.004 mol) of 95% sodium hydroxide and 30 ml of ethanol was stirred at 80°C for 16 hours. After the completion of the reaction, the reaction mixture was filtered to remove inorganic matter. The filtrate was distilled to remove the solvent and the residue was purified by silica gel column chromatography (ethyl acetate/n-hexane) to obtain 1.20 g of the title compound as a white crystal.
^{1}H-NMR(DMSO-d$_6$) δ ; 2.08(s,3H), 3.79(t,J= 6.2Hz,2H), 4.40(t,J=6.2Hz,2H), 4.60(s, 2H), 6.88~7.21(m,3H), 7.22~7.50(m,4H), 7.68~8.02(m,2H), 8.16(d,J=6.2Hz,1H)

Example 69

Sodium salt of 2-[[4-{2-(benzothiazol-2-ylsulfinyl)ethoxy}-3-methylpyridine-2-yl]methylsulfinyl]-1H-benzimidazole

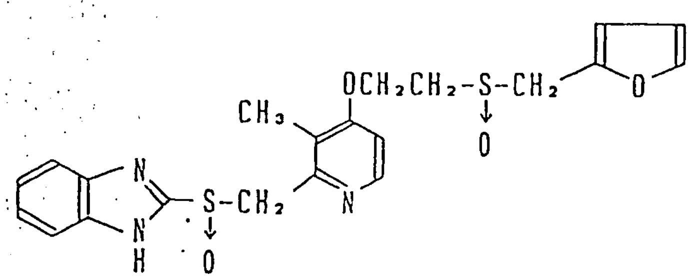


0.93 g (0.002 mol) of 2-[[4-{2-(benzothiazol-2-ylthio)ethoxy}-3-methylpyridine-2-yl]methylthio]-1H-benzimidazole was suspended in 40 ml of dichloromethane. Methanol was added to the obtained suspension until the suspension became transparent. 0.43 g of 80% m-chloroperbenzoic acid was added to the resulting mixture in a nitrogen atmosphere at -60 °C. The obtained mixture was stirred for 0.5 hour. After the completion of the reaction, 0.6 g of triethylamine was added to the reaction mixture and the obtained mixture was heated to -10 °C, followed by the addition of 30 ml of a saturated aqueous solution of sodium hydrogencarbonate. The obtained mixture was stirred at a room temperature for 0.5 hour and extracted with 100 ml of dichloromethane twice. The extract was dried over magnesium sulfate and filtered. The filtrate was distilled to remove the solvent. 0.8 g of the obtained residue was dissolved in 0.1N aqueous sodium hydroxide, followed by the addition of ethanol. The obtained mixture was distilled to remove the solvent. The obtained residue was washed with ether to obtain 0.69 g of the title compound.
^{1}H-NMR(DMSO-d_6) δ ; 2.06(s,3H), 3.66~4.00 (m,2H), 4.19~4.86(m,4H), 6.74~7.04(m, 3H), 7.15 ~7.54(m,4H), 7.64~7.96(m, 2H), 8.21(d,J=6.2Hz,1H)

The following compounds of Examples 70 to 91 were prepared in a similar manner to those described above.

Example 70

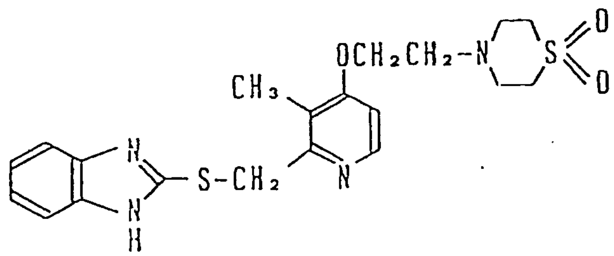
2-[{4-(2-Furanylmethylsulfinyl)ethoxy-3-methylpyridine-2-yl}methylsulfinyl]-1H-benzimidazole



^{1}H-NMR(DMSO-d_6) δ ; 2.36(s,3H), 3.0 ~3.5 (m,2H), 4.0 ~4.6(m,4H), 4.73(s,2H), 6.44(s,2H), 7.02-(d,J=5.4Hz,1H), 7.16~ 7.2(m,2H), 7.28 ~7.76(m,3H), 8.24(d, J =5.4Hz,1H)

Example 71

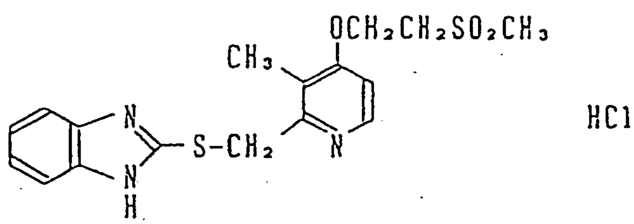
2-[{4-(2-(1,1-Dioxothiomorpholino))ethoxy-3-methylpyridine-2-yl}methylthio]-1H-benzimidazole



^{1}H-NMR(DMSO-d_6) δ ; 2.21(s,3H), 2.99(t,J = 5.8Hz,2H), 3.07(s,8H), 4.16(t,J = 5.8Hz, 2H), 4.68(s,2H), 6.95-(d,J = 6.1Hz,1H), 6.95~7.2(m,2H), 7.3~7.5(m,2H), 8.23 (d,J = 6.1Hz,1H)

Example 72

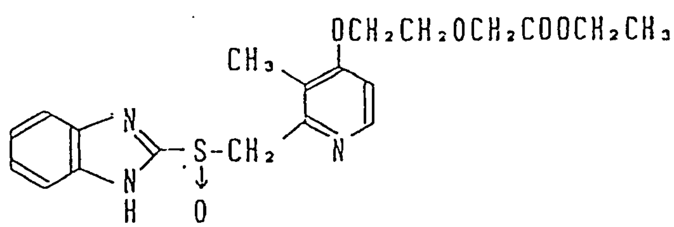
2-[{3-Methyl-4-(2-methylfulfonyl)ethoxy)pyridine-2-yl]methylthio-1H-benzimidazole



^{1}H-NMR(DMSO-d_6) δ ; 2.28(s,3H), 3.08(s,3H), 3.72(t,J = 6.2Hz,2H), 3.66(t,J = 6.2Hz,2H), 3.94(s,2H), 6.8 ~7.6-(m,7H), 8.6(d,J = 5.7Hz,1H)

Example 73

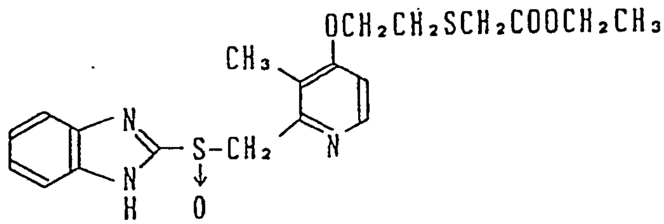
2-[{4-(2-Ethoxycarbonylmethoxy)ethoxy-3-methylpyridine-2-yl}methylsulfinyl]-1H-benzimidazole



^{1}H-NMR(DMSO-d_6) δ ; 1.2((t,J = 7.2Hz,3H), 2.16(s,3H), 3.76~4.32(m,8H), 4.73(s, 2H), 6.94(d,J = 5.4Hz,1H), 7.12~7.4(m, 2H), 7.5~7.7(m,2H), 8.22(d,J = 5.4Hz, 1H)

Example 74

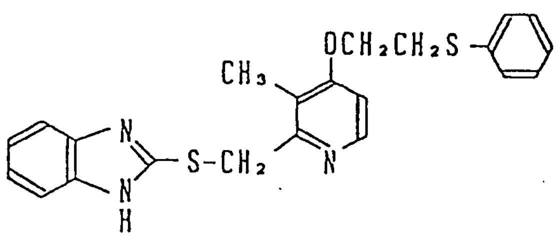
[{4-(2-Ethoxycarbonylsulfinyl)ethoxy-3-methylpyridine 2-yl}methylsulfinyl]-1H-benzimidazole



^{1}H-NMR(DMSO-d$_6$) δ ; 1.22(t,J=7.2Hz,3H), 2.16 (s,3H), 3.16~3.56(m,2H), 3.64~4.6(m, 6H, 4.76(s,2H), 7.04-(d,J=7Hz,1H), 7.16 ~7.24(m,2H), 7.32~7.80(m,2H), 8.24(d, J=7Hz,1H)

Example 75

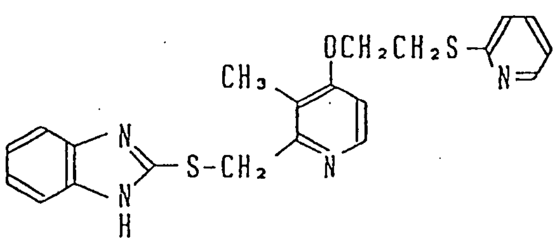
2-[[3-Methyl-4-{(2-phenylthio)ethoxy}pyridine-2-yl]methylthio]-1H-benzimidazole



^{1}H-NMR(CDCl$_3$) δ ;2.08(s,3H), 3.24(t,J=6.1 Hz,2H), 4.06(t,J=6.1Hz,2H), 4.38(s,2H), 6.52(d,J=5.8Hz,1H), 7.04~7.64(m.10H), 8.23(d,J=5.8Hz,1H)

Example 76

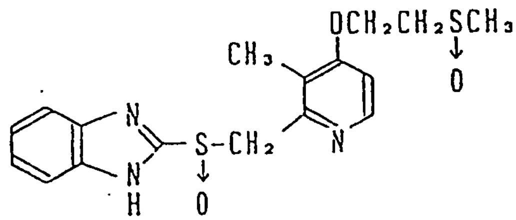
2-[[3-Methyl-4-{(2-pyridylthio)ethoxy}pyridine-2-yl]methylthio]-1H-benzimidazole



^{1}H-NMR(DMSO-d$_6$) δ ;2.14(s,3H), 3.6(t,J= 6.1Hz,2H), 4.32(t,J=6.1Hz,2H), 4.7(s, 2H), 7.0~7.8(m,10H), 8.2 ~8.6(m,2H)

Example 77

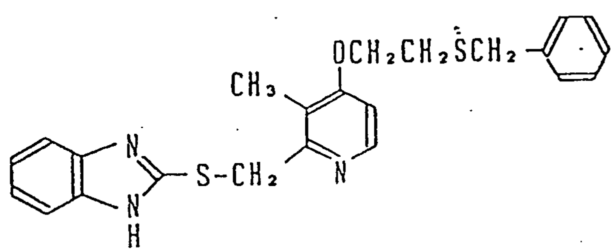
2-[[3-Methyl-4-{(2-methylsulfinyl)ethoxy}pyridine-2-yl]methylsulfinyl]-1H-benzimidazole



^{1}H-NMR(DMSO-d_6) δ ;2.16(s,3H), 2.64(s, 3H), 3.16(m,2H), 4.44(m,2H), 4.78(s, 2H), 7.0(d,J=5.8Hz,1H), 7.4~7.5(m, 2H), 7.5~7.7(m,2H), 8.2(d,J=5.8Hz, 1H)

Example 78

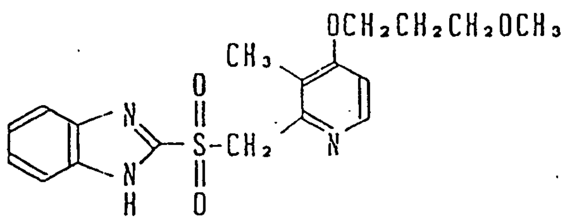
2-[4-{(2-Benzylthio)ethoxy}-3-methylpyridine-2-yl]methylthio]-1H-benzimidazole



^{1}H-NMR(DMSO-d_6) δ ;2.24(s,3H), 2.84(t,J= 5.8Hz,2H), 4.18(t,J=5.8Hz,2H), 4.68(s, 2H), 6.86-(d,J=6.5Hz,1H), 7.0~7.54(m, 9H), 8.23(d,J=6.5Hz,1H)

Example 79

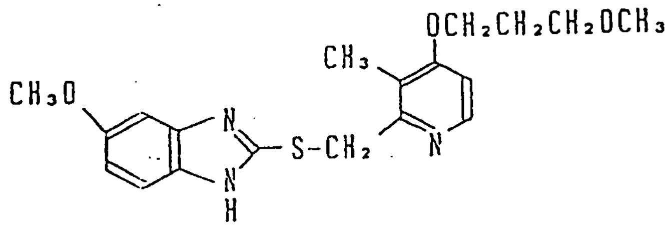
2-[{4-(2-Methoxy)propoxy-3-methylpyridine-2-yl}methylsulfonyl]-1H-benzimidazole



^{1}H-NMR(DMSO-d_6) δ ;2.0(t,J=7.5Hz,2H), 2.2 (s,3H), 3.28(s,3H), 3.5(t,J=7.5Hz,2H), 4.09(t,J=7.5Hz,2H), 5.06(s,2H), 6.92(d, J=5.4Hz,1H), 7.35 ~7.52(m,2H), 7.64~ 7.8(m,2H), 8.03(d,J=5.4Hz,1H)

Example 80

5-Methoxy-2-{4-(3-methoxypropoxy)-3-methylpyridine-2-yl}methylthio-1H-benzimidazole

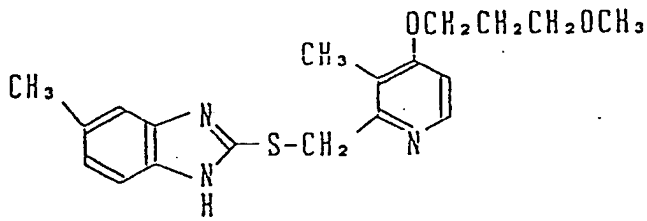


^{1}H-NMR($CDCl_3$) δ;

1.92~2.18(m,2H), 2.22(s,3H), 3.31(s,3H), 3.52(t,J=6.1Hz,2H), 3.80(s,3H), 4.09(t,J=6.1Hz,2H) 4.30(s,2H), 6.64~6.81(m,2H), 6.97(d,J=2.2Hz,1H), 7.33(d,J=8.5Hz), 8.25 (d,J=5.7Hz,1H)

Example 81

5-Methyl-2-{4-(3-methoxypropoxy)-3-methylpyridine-2-yl}methylthio-1H-benzimidazole

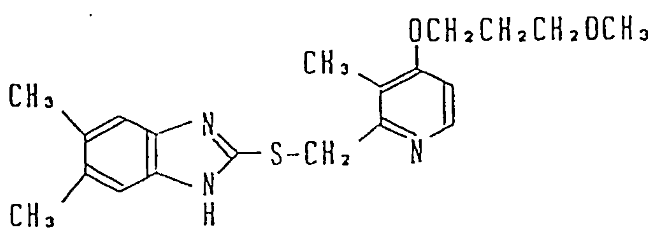


^{1}H-NMR($CDCl_3$) δ ;

1.94~2.19(m,2H), 2.22(s,3H), 2.42(s,3H), 3.31(s,3H), 3.52(t,J=6.1Hz,2H), 4.08(t,J=6.1Hz,2H), 4.31(s,2H), 6.67(d,J=5.7Hz, 1H), 6.80 ~7.00(m,1H), 7.15~7.40-(m,2H), 8.23(d,J=5.7Hz,1H)

Example 82

5,6-Dimethyl-2-{4-(3-methoxypropoxy)-3-methylpyridine-2-yl}methylthio-1H-benzimidazole

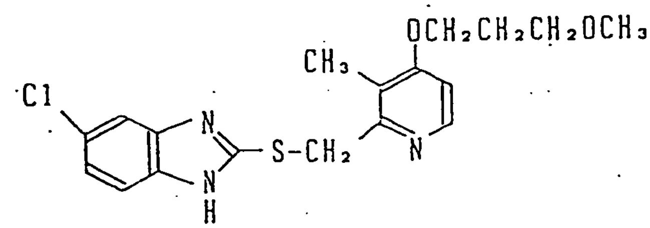


^{1}H-NMR($CDCl_3$) δ ;

1.95~2.17(m,2H), 2.24(s,3H), 2.34(s,6H), 3.35(s,3H), 3.55(t,J=6.2Hz,2H), 4.12(t,J=6.2Hz,2H), 4.35(s,2H), 6.74(d,J=5.7Hz), 7.29(s,2H), 8.32(d,J=5.7Hz)

Example 83

5-Chloro-2-{4-(3-methoxypropoxy)-3-methylpyridine-2-yl}methylthio-1H-benzimidazole

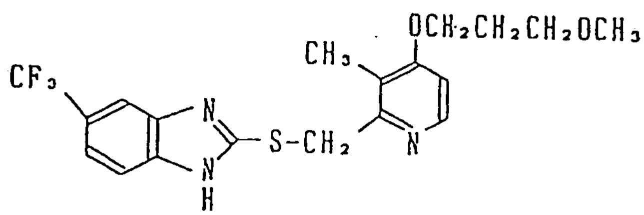


^{1}H-NMR($CDCl_3$) δ ;

1.93~2.18(m,2H), 2.25(s,3H), 3.35(s,3H), 3.56(t,J=6,2Hz,2H), 4.13(t,J=6.2Hz,2H), 4.36(s,2H), 6.76(d,J=5.7Hz,1H), 7.10(dd, J=8.8Hz,2.2Hz,1H), 7.42-(d,J=8.8Hz,1H), 7.50(d,J=2.2Hz,1H), 8.31(d,J=5.7Hz,1H)

Example 84

2-{4-(3-Methoxypropoxy)-3-methylpyridine-2-yl}methylthio-5-trifluoromethyl-1H-benzimidazole

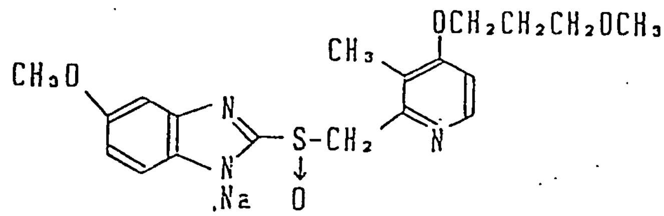


^{1}H-NMR($CDCl_3$) δ ;

1.92~2.19(m,2H), 2.27(s,3H), 3.36(s,3H), 3.56(t,J=5.9Hz,2H), 4.15(t,J=6.1Hz,2H), 4.38(s,2H), 6.79(d,J=5.7Hz,1H), 7.23~ 7.60(m,2H), 7.71(s,1H), 8.35(d,J=5.7Hz, 1H)

Example 85

Sodium salt of 5-methoxy-2-{4-(3-methoxypropoxy)-3-methylpyridine-2-yl}methylsulfinyl-1H-benzimidazole

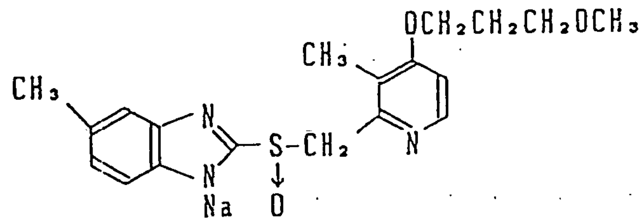


^{1}H-NMR(DMSO-d_6) δ ;

1.84~2.06(m,2H), 2.14(s,3H), 3.25(s,3H), 3.49(t,J=6.2Hz,2H), 3.72(s,3H), 4.09-(t,J =6.2Hz,2H), 4.53(ABq,J=12.7Hz, $\Delta\nu$=18.0Hz, 2H), 6.54-(dd,J=8.8Hz,2.6Hz,1H), 6.91(d,J =5.7Hz,1H), 7.00(d,J=2.6Hz,1H), 7.34(d,J =8.8Hz,1H), 8.27(d,J=5.7Hz,1H)

Example 86

Sodium salt of 5-methyl-2-{4-(3-methoxypropoxy)-3-methylpyridine-2-yl}methylsulfinyl-1H-benzimidazole

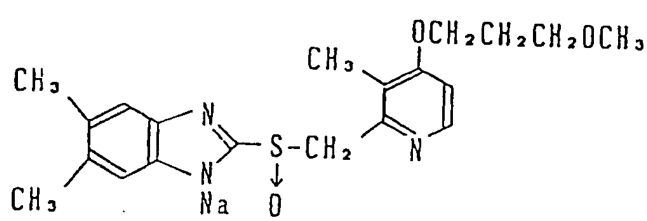


^{1}H-NMR(DMSO-d_6) δ ;

1.84~2.05(m,2H), 2.14(s,3H), 2.37(s,3H), 3.25(s,3H), 3.48(t,J=6.2Hz,2H), 4.09-(t,J =6.2Hz,2H), 4.53(ABq,J=12.8Hz, $\Delta\nu$=17.3 Hz,2H), 6.71-(dd,J=7.9Hz,1.5Hz,1H), 6.91 (d,J=5.7Hz,1H), 7.26(s,1H), 7.35(d,J=7.9 Hz,1H), 8.27(d,J=5.7Hz,1H)

Example 87

Sodium salt of 5,6-dimethyl-2-{4-(3-methoxyporpoxy)-3-methylpyridine-2-yl}methylsulfinyl-1H-benzimidazole

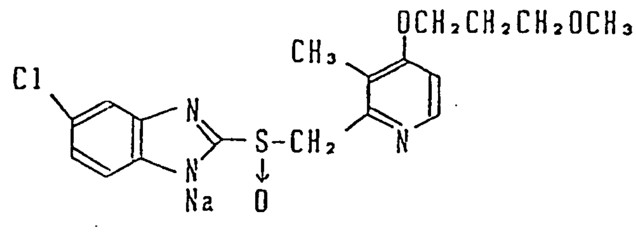


^{1}H-NMR(DMSO-d_6) δ ;

1.82~2.08(m,2H), 2.13(s,3H), 2.27(s,6H), 3.24(s,3H), 3.47(t,J = 6.6Hz,2H), 4.08-(t,J = 6.7Hz,2H), 4.54(ABq,J = 13.0Hz, Δ ν = 19.8 Hz,2H), 6.90(d,J = 5.7Hz,1H), 7.25(s,2H), 8.26(d,J = 5.7Hz,1H)

Example 88

Sodium salt of 5-chloro-2-{4-(3-methoxypropoxy)-3-methylpyridine-2-yl}methylsulfinyl-1H-benzimidazole

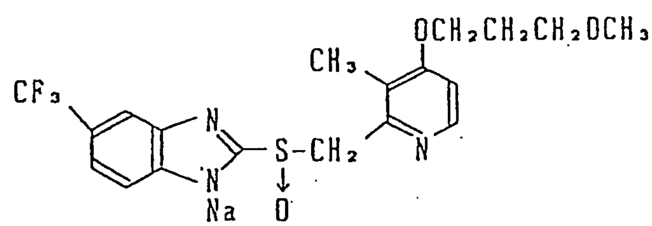


^{1}H-NMR(DMSO-d_6) δ ;

1.80~2.06(m,2H), 2.13(s,3H), 3.25(s,3H), 3.48(t,J = 6.2Hz,2H), 4.09-(t,J = 6.2Hz,2H), 4.54(ABq,J = 12.9Hz, Δ ν = 15.3Hz,2H), 6.65 ~6.92(m,2H), 7.25~7.50(m,2H), 8.27(d,J = 5.3Hz)

Example 89

Sodium salt of 2-{4-(3-methoxypropoxy)-3-methylpyridine-2-yl}methylsulfinyl-5-trifluoromethyl-1H-benzimidazole

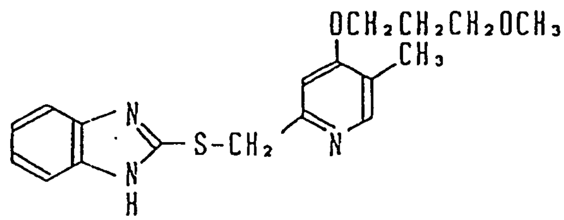


^{1}H-NMR(DMSO-d_6) δ ;

1.84~2.06(m,2H), 2.14(s,3H), 3.25(s,3H), 3.48(t,J = 6.2Hz,2H), 4.09-(t,J = 6.1Hz,2H), 4.56(ABq,J = 13.2Hz, Δ ν = 13.5Hz,2H), 6.92 (d,J = 5.3Hz,1H), 7.01~7.22(m,1H), 7.45~ 7.82(m,2H), 8.21(d,J = 5.3Hz,1H)

Example 90

2-{4-(3-Methoxypropoxy)-5-methylpyridine-2-yl}methylthio-1H-benzimidazole

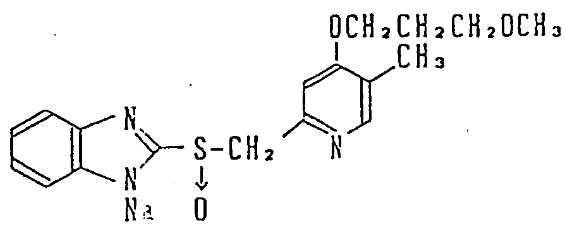


^{1}H-NMR($CDCl_3$) δ ;

1.90~2.24(m,2H), 2.16(s,3H), 3.31(s,3H), 3.51(t,J=6.2Hz,2H), 4.08(t,J=6.2Hz,2H), 4.22(s,2H), 6.74(s,1H), 6.99~7.22(m,2H), 7.32~7.58(m,2H), 8.16(s,1H)

Example 91

Sodium salt of 2-{4-(3-methoxypropoxy)-5-methylpyridine-2-yl}methylsulfinyl-1H-benzimidazole

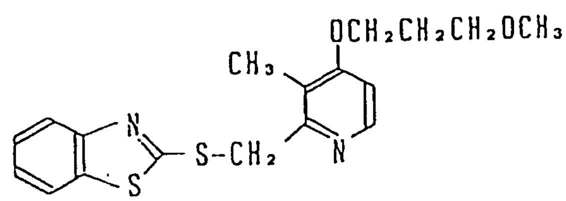


^{1}H-NMR(DMSO-d_6) δ ;

1.56~1.87(m,2H), 2.00(s,3H), 3.16(s,3H), 3.20~3.72(m,4H), 6.16~6.60(m,2H), 6.49 (s,1H), 6.68~6.92(m,2H), 7.28~7.50(m, 2H), 8.13(s,1H)

Example 92

2-{4-(3-Methoxypropoxy)-3-methylpyridine-2-yl}methylthio-benzothiazole



A mixture comprising 0.8 g of 2-chloromethyl-4-(3-methoxypropoxy)-3-methylpyridine hydrochloride, 0.5 g of 2-mercaptobenzothiazole, 0.36 g of sodium hydroxide and 30 ml of ethanol was stirred at a room temperature for 6 hours and distilled under a reduced pressure to remove the ethanol. The residue was purified by silica gel column chromatography to obtain 0.85 g of the title compound as a pale yellow crystal.

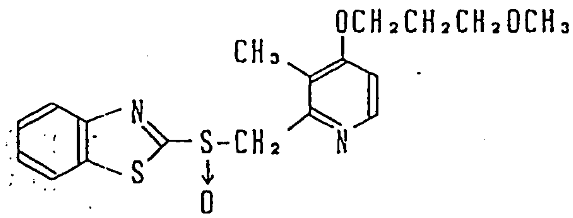
^{1}H-NMR($CDCl_3$) δ ;

1.9 ~2.2(m,2H), 2.30(s,3H), 3.35(s,3H), 3.56(t,J=6.1Hz,2H), 4.10(t,J=6.1Hz,2H),

4.81(s,2H), 6.70(d,J=5.7Hz,1H), 7.1 ~ 7.5(m,2H), 7.5~7.9(m,2H), 8.29(d,J=5.7 Hz,1H)

Example 93

2-{4-(3-Methoxypropoxy)-3-methylpyridine-2-yl}methylsulfinylbenzothiazole



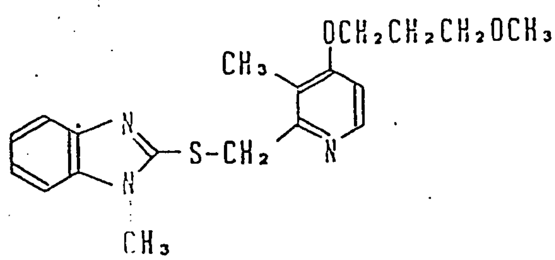
0.6 g of 2-{4-(3-methoxypropoxy)-3-methylpyridine-2-yl}methylthiobenzothiazole was dissolved in 20 ml of dichloromethane to obtain a solution. 0.36 g of 80% m-chloroperbenzoic acid was added to the solution at -45°C. After one hour, 0.34 g of triethylamine and 30 ml of a saturated aqueous solution of sodium hydrogencarbonate were added to the obtained mixture. The resulting mixture was stirred at a room temperature for 30 minutes. The dichloromethane layer was separated, washed with a saturated aqueous solution of sodium hydrogencarbonate twice, dried over magnesium sulfate and filtered. The filtrate was concentrated to obtain a residue. This residue was purified by silica gel column chromatography to obtain 0.17 g of the title compound as a white crystal.

^{1}H-NMR(CDCl$_3$) δ ;

1.95~2.18(m,2H), 2.20(s,3H), 3.34(s,3H), 3.54(t,J=6.1Hz,2H), 4.10(t,J=6.1Hz,2H), 4.67(s,2H), 6.71(d,J=5.7Hz,1H), 7.40~7.0 (m,2H), 7.92~8.20(m,2H), 8.25-(d,J=5.7Hz, 1H)

Example 94

2-{4-(3-Methoxypropoxy)-3-methylpyridine-2-yl}methylthio-1-methylbenzimidazole



0.5 g of 2-{4-(3-hydroxypropoxy)-3-methylpyridine-2-yl}methylthio-1H-benzimidazole was dissolved in 30 ml of dimethylformamide to obtain a solution. 0.24 g of 60% sodium hydride was added to the solution at 0°C. The obtained mixture was stirred at 40°C for one hour and cooled again to 0°C, followed by the addition of 0.5 g of methyl iodide. The obtained mixture was stirred at a room temperature for 3 hours. Then, a saturated aqueous solution of ammonium chloride was added to the resulting mixture to stop the reaction. The reaction mixture was distilled under a reduced pressure to remove the solvent and the residue was purified by silica gel column chromatography to obtain 0.3 g of the title compound as a pale yellow crystal.

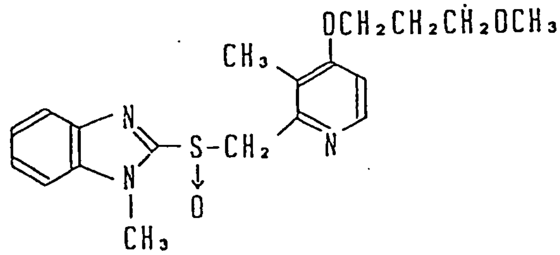
^{1}H-NMR(CDCl$_3$) δ ;

1.95~2.21(m,2H), 2.30(s,3H), 3.35(s,3H), 3.54(t,J=6.2Hz,2H), 3.67(s,3H), 4.10(t,J=6.2Hz,2H), 4.80(s,2H), 6.68(d,J=5.7Hz, 1H), 7.16 ~7.30(m,3H), 7.57~7.80-

(m,1H), 8.29(d,J=5.7Hz,1H)

Example 95

2-{4-(3-Methoxypropoxy)-3-methylpyridine-2-yl}methylsulfinyl-1-methylbenzimidazole



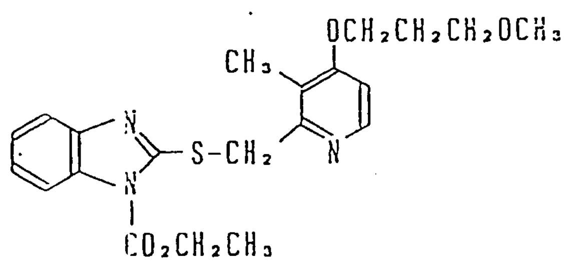
0.25 g of 2-{4-(3-methoxypropoxy)-3-methylpyridine-2-yl}methylthio-1-methylbenzimidazole was dissolved in 20 ml of dichloromethane to obtain a solution. 0.18 g of 80% m-chloroperbenzoic acid was added to the solution at -50 °C. The obtained mixture was stirred for one hour, followed by the addition of 0.14 g of triethylamine and 20 ml of a saturated aqueous solution of sodium hydrogencarbonate. The obtained mixture was stirred at a room temperature for one hour. The dichloromethane layer was separated, washed with a saturated aqueous solution of sodium hydrogencarbonate twice, dried over magnesium sulfate and filtered. The filtrate was concentrated to obtain a residue. This residue was purified by silica gel column chromatography to obtain 0.12 g of the title compound as a pale yellow crystal.

^{1}H-NMR(CDCl$_3$) δ ;

1.98~2.12(m,2H), 2.22(s,3H), 3.33(s,3H), 3.53(t,J=6.2Hz,2H), 3.98(s,3H), 4.06(t,J=6.2Hz,2H), 4.96(s,2H), 6.65(d,J=5.7Hz, 1H), 7.25 ~7.40(m,3H), 7.75~7.87-(m,1H), 8.15(d,J=5.7Hz,1H)

Example 96

1-Ethoxycarbonyl-2-{4-(3-methylpropoxy)-3-methylpyridine-2-yl}methylthiobenzimidazole



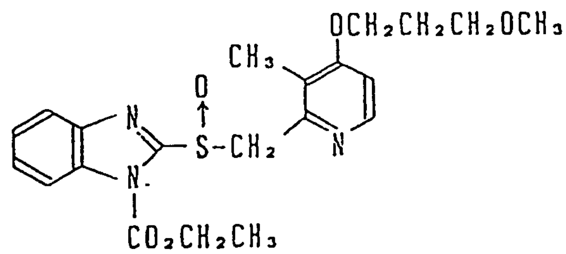
0.8 g of 2-{4-(3-methoxypropoxy)-3-methylpyridine-2-yl}methylthio-1H-benzimidazole was dissolved in 10 ml of dimethylformamide to obtain a solution. 0.23 g of 60% sodium hydride was added to this solution at 0 °C. The obtained mixture was stirred for 15 minutes. 0.4 g of ethyl chlorocarbonate was dropwise added to the resulting mixture at 0 °C. The obtained mixture was stirred at a room temperature for one hour. A saturated aqueous solution of ammonium chloride was added to the resulting mixture to stop the reaction. The reaction mixture was extracted with chloroform. The extract was dried over magnesium sulfate and filtered. The filtrate was concentrated to obtain a residue. This residue was purified by silica gel column chromatography to obtain 0.82 g of the title compound as a white crystal.

^{1}H-NMR(CDCl$_3$) δ ;

1.50(t,J=7.0Hz,3H), 1.95~2.20(m,2H), 2.32(s,3H), 3.36(s,3H), 3.56(t,J=6.2Hz, 2H), 4.10(t,J=6.2Hz,2H), 4.54(q,J=7.0Hz, 2H), 4.77(s,2H), 6.69(d,J=5.7Hz,1H), 7.1~7.4(m,2H), 7.4~7.7(m,1H), 7.7~7.95(m, 1H), 8.30(d,J=5.7Hz,1H)

Example 97

1-Ethoxycarbonyl-2-{4-(3-methoxypropoxy)-3-methylpyridine-2-yl}methylsulfinylbenzimidazole



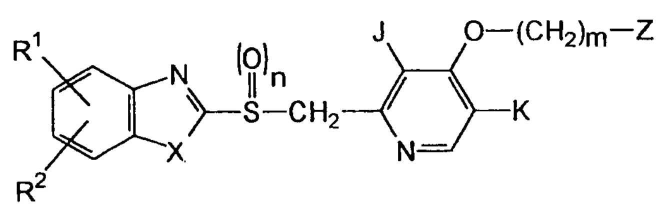
0.6 g of 1-ethoxycarbonyl-2-{4-(3-methoxypropoxy)-3-methylpyridine-2-yl}methylthiobenzimidazole was dissolved in 20 ml of dichloromethane to obtain a solution. 0.4 g of m-chloroperbenzoic acid was added to the solution at -45°C. After one hour, 0.3 g of triethylamine and 20 ml of a saturated aqueous solution of sodium hydrogencarbonate were added to the resulting mixture. The obtained mixture was stirred at a room temperature for 30 minutes. The dichloromethane layer was separated, washed with a saturated aqueous solution of sodium hydrogencarbonate twice, dried over magnesium sulfate and filtered. The filtrate was concentrated to obtain a residue. This residue was purified by silica gel column chromatography to obtain 0.21 g of the title compound as a yellow oil.

^{1}H-NMR($CDCl_3$) δ ;

1.54(t,J=7.0Hz,3H), 1.99~2.20(m,2H), 2.30(s,3H), 3.35(s,3H), 3.55(t,J=6.2Hz, 2H), 4.06(t,J=6.2Hz,2H), 4.61(q,J=7.0Hz, 2H), 4.74(ABq,J=12.8Hz, Δν=8.6Hz,2H), 6.60(d,J=5.7Hz,1H), 7.3 ~7.5(m,2H), 7.7 ~8.0(m,2H), 8.03-(d,J=5.7Hz,1H)

Claims

1. A pyridine derivative represented by the general formula:



wherein R^1 and R^2 may be the same or different from each other and each stand for a hydrogen atom, a C_{1-6} alkyl, C_{1-6} alkoxy, halogenated C_{1-6} alkyl, (C_{1-6} alkoxy)carbonyl or carboxyl group or a halogen atom; X stands for a group represented by the formula: -O-, -S- or

$$\begin{array}{c} -N- \\ | \\ R^3 \end{array}$$

(wherein R^3 stands for a hydrogen atom or a C_{1-6} alkyl, phenyl, benzyl or (C_{1-6} alkoxy)carbonyl group);
Z stands for
① a group represented by the general formula:

$-O-(CH_2)_q-R^5$

wherein q stands for an integer of 1 to 3 and R^5 stands for a naphthyl group, which may be substituted with a C_{1-6} alkoxy group, a hydroxyl group or a halogen atom; a pyridyl group or a furyl group,
② a group represented by the general formula:

$-OR^9$

wherein OR^9 stands for a phenyl, tolyl, xylyl or naphthyl group,
n stands for an integer of 0 to 2; m stands for an integer of 2 to 10; and
J and K may be the same or different from each other and each stand for a hydrogen atom or a C_{1-6} alkyl group, and a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein Z represents a group selected from category 1.

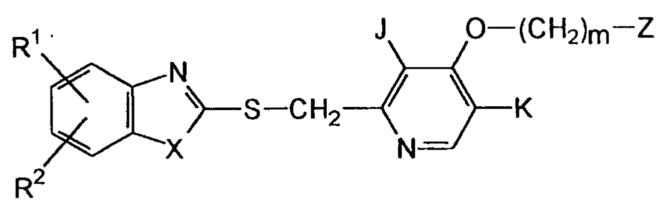
3. A pharmaceutical composition which comprises a pharmacologically effective amount of a pyridine derivative according to claim 1 or 2 or a pharmacologically acceptable salt thereof and a pharmacologically acceptable carrier.

4. A pharmaceutical composition according to claim 3 which comprises 0.1 to 100 g of the pyridine derivative or a pharmacologically acceptable salt thereof per unit dose.

5. A pharmaceutical composition according to claim 3 or 4 for the treatment or prevention of peptic ulcers.

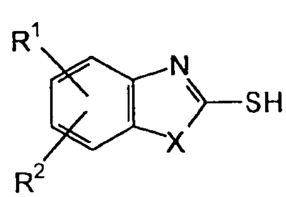
6. The use of a pyridine derivative according to claim 1 or 2 for the manufacture of a medicament for the treatment or prevention of peptic ulcers.

7. A process for producing a compound of general formula I':



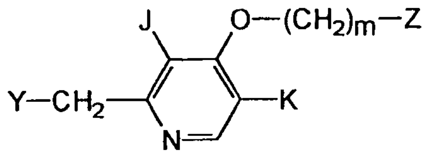
(I')

wherein R^1, R^2, X, J, K, Z and m are as defined in claim 1,
or a pharmaceutically acceptable salt thereof,
comprising the step of reacting the compound of formula II with the compound of formula III



(II)

wherein R^1, R^2 and X are as defined above



(III)

wherein m, Z, J and K are as defined above and Y represents a halogen atom or a sulfonyloxy group,
and optionally converting the product into a salt.

8. A process according to claim 7, wherein Y represents chlorine, bromine or iodine.

9. A process according to claim 7, wherein Y represents an alkyl sulfonyloxy group.

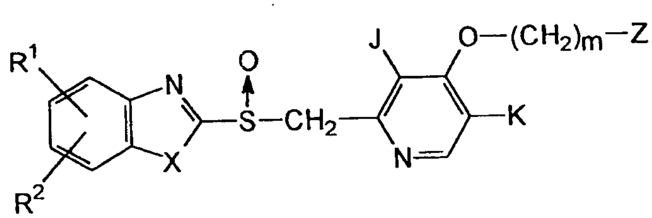
10. A process according to claim 9, wherein the alkyl sulfonyloxy group is a methyl sulfonyloxy group or an ethyl sulfonyloxy group.

11. A process according to claim 9, wherein the sulfonyloxy group is an aromatic sulfonyloxy group.

12. A process according to claim 11, wherein the aromatic sulfonyloxy group is a benzene sulfonyloxy group or a tosyloxy group.

13. A process according to any of claims 7 to 12, wherein the reaction is carried out in the presence of an acid scavenger.

14. A process for producing a compound of formula I'':

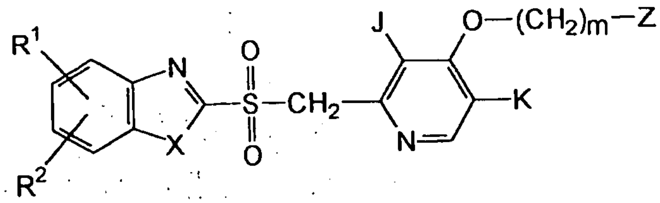


(I'')

wherein R^1, R^2, X, J, K, Z and m are as defined in claim 1,
or a pharmaceutically acceptable salt thereof,
comprising the step of reacting the compound of formula I' as defined in claim 7 with an approximately equimolar amount of an oxidizing agent, and optionally converting the product into a salt.

15. A process according to claim 14, wherein the oxidizing agent is selected from hydrogen peroxide, peracetic acid, m-chloroperbenzoic acid, sodium hypochlorite or sodium hypobromite.

16. A process for producing a compound of formula I''':

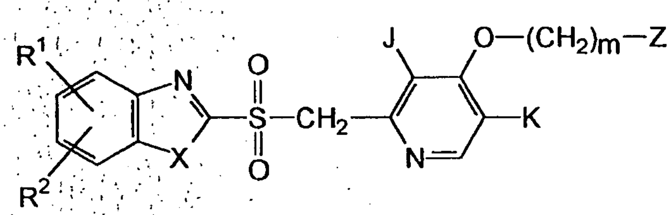


(I''')

wherein R^1, R^2, X, J, K, Z and m are as defined in claim 1,
or a pharmaceutically acceptable salt thereof,
comprising the step of reacting the compound of formula I' as defined in claim 7 with at least two molar equivalent amounts of an oxidizing agent, and optionally convering the product into a salt.

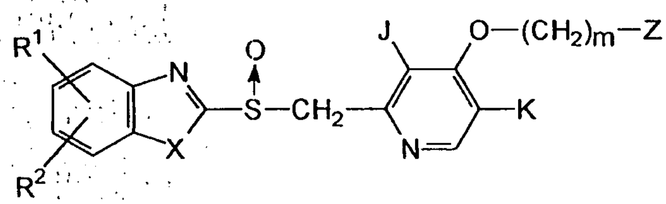
17. A process according to claim 16, wherein the oxidizing agent is selected from hydrogen peroxide, peracetic acid, m-chloroperbenzoic acid, sodium hypochlorite or sodium m-periodate.

18. A process for producing the compound of formula I''':



(I''')

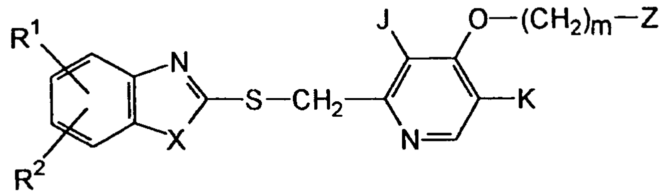
wherein R^1, R^2, X, J, K, Z and m are as defined in claim 1,
or a pharmaceutically acceptable salt thereof,
comprising the step of reacting an oxidizing agent with a compound of formula I'':



(I'')

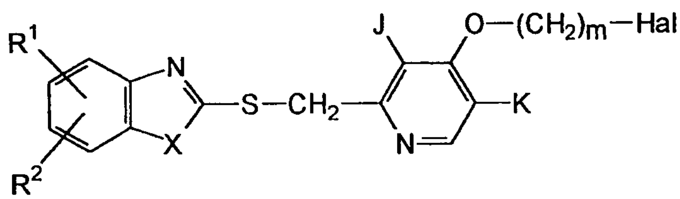
wherein R^1, R^2, X, J, K, Z and m are as defined above,
and optionally converting the product into a salt.

19. A process for producing a compound of formula I':



(I')

wherein R^1, R^2, X, J, K, Z and m are as defined in claim 1, or a pharmaceutically acceptable salt thereof,
comprising the step of reacting a compound of formula IV:

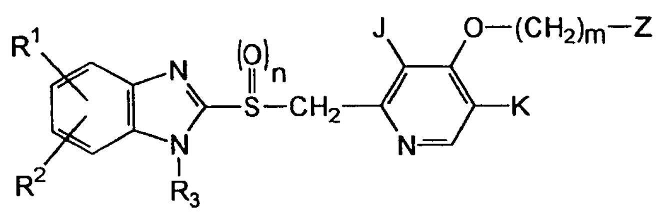


(IV)

wherein R^1, R^2, X, K, J and m are as defined above and Hal represents a halogen atom, with a compound of formula Z-H, wherein Z is as defined above,
and optionally converting the product into a salt.

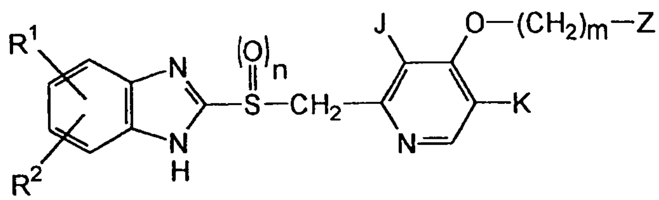
20. A process according to claim 19, wherein the reaction is carried out in the presence of an acid scavenger.

21. A process for producing a compound of formula I'''':



(I'''')

wherein R^1, R^2, n, J, K, m and Z are as defined in claim 1 and R^3 represents a C_{1-6} alkyl, phenyl, benzyl or (C_{1-6} alkoxy)carbonyl group,
or a pharmaceutically acceptable salt thereof,
comprising the step of reacting the compound of formula VI:



(VI)

wherein R^1, R^2, n, J, K, m and Z are as defined above,
with R^3Hal, wherein Hal represents a halogen atom, and optionally converting the product into a salt.

22. A process according to claim 21, which is carried out in the presence of a dehydrohalogenating agent.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 95 10 2165

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.4)
D,X	EP-A-0 167 943 (BEECHAM GROUP PLC) * claims 1-10,13,14 * ---	1,3-6	C07D401/12 A61K31/44 C07D401/14 C07D405/14 C07D413/12 C07D417/12
A	EP-A-0 173 664 (AKTIEBOLAGET HÄSSLE) * claims 1,7-11 * -----	1-6	

TECHNICAL FIELDS SEARCHED (Int.Cl.4)

C07D

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	14 March 1995	Henry, J

CATEGORY OF CITED DOCUMENTS

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21

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

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(21) Application number: 95102165.8

(22) Date of filing: 13.11.1987

(54) Pyridine derivatives, pharmaceutical compositions comprising the same, the use of the same for the manufacture of medicaments having therapeutic or preventative value, and process for preparing the same

Pyridin-Derivate, deren pharmazeutische Zusammenstellungen, deren Anwendung für die Herstellung von Arzneimitteln mit therapeutischem oder vorbeugendem Wert und Verfahren zu deren Herstellung

Dérivés de pyridine, compositions pharmaceutiques les contenant, leur utilisation pour le préparation de médicaments de valeur thérapeutique ou préventive et procédé pour leur préparation

(84) Designated Contracting States:
AT BE CH DE ES FR GB GR IT LI LU NL SE

(30) Priority: 13.11.1986 JP 270536/86
02.02.1987 JP 21989/87
31.03.1987 JP 77784/87

(43) Date of publication of application:
24.05.1995 Bulletin 1995/21

(62) Document number(s) of the earlier application(s) in accordance with Art. 76 EPC:
91117132.0 / 0 475 456
87116797.9 / 0 268 956

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(56) References cited:
EP-A- 0 167 943 EP-A- 0 173 664

Remarks:
The file contains technical information submitted after the application was filed and not included in this specification

EP 0 654 471 B1

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Description

TECHNICAL FIELD

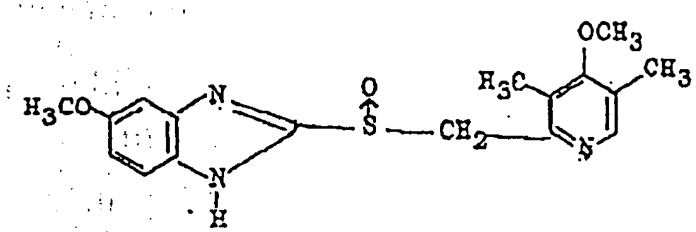
Novel pyridine derivatives exhibiting activity in treating or preventing peptic ulcers, pharmaceutical compositions containing them, and methods of medical treatment are described.

BACKGROUND ART

Duodenal and gastric ulcers, known collectively as peptic ulcers, are localized erosions of the mucous membrane of the duodenum or stomach, respectively, which expose the underlying layers of the gut wall to the acid secretions of the stomach and to the proteolytic enzyme pepsin. They are believed to be caused by autolysis which is caused by an imbalance between offensive factors, such as acid or pepsin, and defensive factors, such as resistance of the mucous membrane, mucilage secretion, bloodstream or control of the duodenum. Peptic ulceration is the most common disease of the gastro-intestinal tract and it is estimated that approximately 10 to 20% of the adult male population will experience at some time in their lives.

Peptic ulcers are cured or prevented by medical treatment, in principle, and many pharmacotherapies have been suggested, some with high degrees of success.

Clinically useful modialities include H_2-blockers, such as cimetidine and ranitidine, as anti-ulcer agents. It has been noted, more recently, that inhibitors of H^+-K^+-ATPase, an enzyme specifically present in the parietal cells of the stomach, can effectively inhibit the secretion of gastric acid in mammals, including man, therefore it has been expected that a new class of anti-ulcer agents from this viewpoint will come into existance. More specifically, a wide variety of compounds having a benzimidazole structure have been proposed. Among these compounds is Omeprazole, currently under active development, as the most promising compound; see U.S. Patent Nos. 4,337,257; 4,255,431; and 4,508,905. These patents describe compounds with a methoxy group in the 4-position of the pyridine ring. Omeprazole, having the formula:



and further 2-(4-methoxyethoxypyridine-2-yl)-methylsulfinyl-5-methyl-1H-benzimidazole in the working examples thereof.

Related benzyimidazole-type compounds having anti-ulcer activities are described in published application GB 2,134,523A. More specifically, compounds in Which the 4-position of the pyridine ring is substituted with an alkoxyalkoxy group with each alkoxy group containing 1-2 carbons are described. Example 157 of this patent describes 2-(3,5-dimethyl-4-methoxyethoxypyridine-2-yl)methylsulfinyl-5-phenyl-1H-benzimidazole. Other substitutions on various positions of the benzyl and pyridine rings are also described.

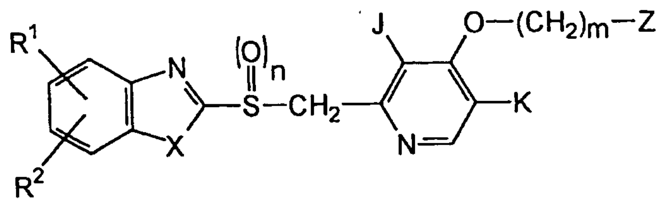
Biological tests reported in tables 4 and 5 of this published application report significant biological effects on gastric acid secretion, both in isolated cells and in laboratory animals, when the 4-position on the pyridine ring is substituted with a methoxy group.

Additional benzimidazole-type compounds, in which the substituent at the 4-position on the pyridine ring is a benzyloxy group, are described in European patent application 0,167,943.

DISCLOSURE OF THE INVENTION

The present inventors have discovered a class of novel compounds with a more excellent anti-ulcer activity than Omeprazole which is regarded, at the present time, as the most significant benzimidazole-type compound having anti-ulcer activity. As a result of intensive studies, it has been found that compounds represented by formula (I) are more potent in Inhibiting gastric acid secretion in comparison with Omeprazole. The present invention has been accomplished on the basis of this finding.

The present invention includes a class of pyridine derivatives represented by the general formula (I):



(I)

wherein R^1 and R^2 may be the same or different from each other and each stand for a hydrogen atom, a C_{1-6} alkyl, C_{1-6} alkoxy, halogenated C_{1-6} alkyl, (C_{1-6} alkoxy)carbonyl or carboxyl group or a halogen atom; X stands for a group represented by the formula: -O-, -S- or

$$-\underset{\underset{R^3}{|}}{N}-$$

(wherein R^3 stands for a hydrogen atom or a C_{1-6} alkyl, phenyl, benzyl or (C_{1-6} alkoxy)carbonyl group);

Z stands for
a group represented by the general formula:

$$-O-(CH_2)_q-R^5$$

wherein q stands for an integer of 1 to 3 and R^5 stands for a naphthyl group, which may be substituted with a C_{1-6} alkoxy group, a hydroxyl group or a halogen atom; a pyridyl group or a furyl group,
n stands for an integer of 0 to 2; m stands for an integer of 2 to 10; and
J and K may be the same or different from each other and each stand for a hydrogen atom or a C_{1-6} alkyl group, and a pharmaceutically acceptable salt thereof.

The same definitions for R^1, R^2, X, n, J, K, Z and m are used throughout the specification that follows and in the appended claims.

Also disclosed are pharmaceutical compositions containing these compounds as the active ingredient(s) and procedures for preventing or treating peptic ulcers in mammals, including humans, using these pharmaceutical compositions.

In the definition of the compounds of general formula (I) given above, the C_{1-6} alkyl group defined above with respect to R^1, R^2, R^3, R^4, R^6, A, R^7, R^8, J and K in the compound (I) of the present invention nay be a straight-chain or branched alkyl groups having 1 to 6 carbon atoms. Examples include methyl, ethyl, n-propyl, n-butyl, isopropyl, isobutyl, 1-methylpropyl, tert-butyl, n-pentyl, 1-ethylpropyl, isoamyl and n-hexyl groups, among which methyl and ethyl groups are most preferred.

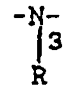
The C_{1-6} alkoxy group and the C_{1-6} alkoxy moiety of the C_{1-6} alkoxycarbonyl group defined above with respect to R^1 and R^2 may be an alkoxy group derived form the above C_{1-6} alkyl group. Methoxy and ethoxy groups are most preferred.

The halogen atom defined above includes chlorine, bromine, iodine or fluorine. R^5 means naphthyl which may be substituted with a C_{1-6} alkoxy, hydroxyl group or a halogen atom, or R^5 includes pyridyl and furyl groups.

As for R^1 and R^2, hydrogens for both and then a combination of a C_{1-6} alkyl, inter alia methyl, for R^1 and hydrogen for R^2 are preferred. X is preferably -NR^3 where R^3 is hydrogen. A preferred value for n is 1. The preferred substituents for J and K are both hydrogen or where J is C_{1-6} alkyl, inter alia methyl, and K is hydrogen, or when J is hydrogen K is C_{1-6} alkyl, inter alia methyl. Thus, J or K are independently preferably hydrogen or methyl, most preferably J is methyl and K is hydrogen.

Examples of the pharmaceutically acceptable salt include salts with inorganic acids, such as hydrochloride, hydrobromide, sulfate and phosphate; those with organic acids, such as acetate, malcate, tartrate, methanesulfonate, benzenesulfonate, and toluenesulfonate; and those with amino acids such as arginine, aspartic acid and glutamic acid.

Some of the compounds according to the present invention can form a salt with a metal such as Na, K, Ca or Mg. These metal salts are also included among the pharmaceutically acceptable salts of the present invention. For example, compounds represented by the general formula (I), wherein X is a group of



and R^3 is a hydrogen atom can be present as a metal salt.

Although the compounds of the present invention may also be present as a hydrate or as a stereoisomer, it is a matter of course that these hydrates and stereoisomers are also included in the scope of the present invention.

Now, the effect of the compounds of the present invention will be described by referring to the following pharmacological experiments.

Pharmacological Experiment

Inhibition against the activity of H^+-K^+ ATPase

(1) Preparation of H^+-K^+ ATPase

Prepared from the fundic glands of a fresh mucous membrane of a pig stomach according to a modified method of Saccomani et al. (see Biochem. and Biophys. Acta, 464, 313 (1977)).

(2) Measurement of the activity of H^+-K^+ ATPase

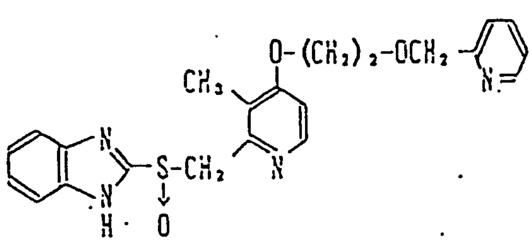
The compound of the present invention was incubated at various concentration in a 40 mM Tris-HCl buffer solution having a pH of 7.40 together with H^+-K^+ ATPase and 10 μg/ml of a protein at 37°C for 30 minutes, followed by the addition of 15 mM KCl. After 10 minutes, the ATPase reaction was initiated by the addition of 3 mM of $MgCl_2$ and ATP. After 10 minutes, the amount of the released inorganic phosphoric acid was determined according to the method of Yoda and Hokin (see Biochem. Biophys. Res. Com., 40, 880 (1970)).

The test compound was used as a solution in methanol.

The inhibitory effect was determined by subtracting the amount of the released inorganic acid observed with respect to the case wherein a solution of a test compound was added from that with respect to the control wherein only a solvent was added to determine a difference and dividing this difference by the latter amount and shown by percentage. The inhibitory effect is shown in Table 1 in terms of IC_{50}.

(3) The results are shown in Table 1.

Table 1

No.	Compound (Example 2)	IC_{50} (M)
1		1.2×10^{-6}

It is apparent from the results of the experiments that the compound of the present invention exhibits a high inhibitory effect on the activity of H^+-K^+ ATPase and is highly safe, so that it can effectively inhibit the secretion of an acid

and is therefore effective in the therapy or prevention of human and animal peptic ulcer.

Further, it should be noted that the compound of the present invention unexpectedly exhibits a faster recovery or resumption of gastric acid secretion than Omeprazole.

At present, this H^+-K^+ATPase-inhibiting agent is believed to have a more potent inhibitory activity against gastric acid secretion than an H_2-blocker compound, and thus, in the future, may be the drug of choice for the treatment of ulcers.

But, while more potent inhibitory activity against gastric acid secretion is desirable, too long-lasting inhibition of gastric acid secretion is not preferable for an anti-ulcer agent. For example, it gives rise to the proliferation of Enterochromaffin-like cells (ECL cell) and formation of carcinoid derived from hypergastrinemia; see "Digestion", vol. 35, suppl. 1, page 42 to 55 (1986); the increase in the gastric bacterial flora and endogenous production of N-nitro compounds; see "Brit. Med. J.", vol. 289, page 717 (1984); and difficulty in determining the appropriate dosage regimen.

Thus, an H^+-K^+ATPase-inhibitory agent which possesses an excellent recovery of gastric acid secretion is most preferred.

The compounds of the present invention are administered for the therapy or prevention of peptic ulcers either orally as powders, granules, capsules or syrup, or parenterally as an injection, or as an external preparation or drop, or as a suppository. Although the dose remarkably varies depending upon symptoms, age or kind of ulcer(s), it may be about 0.01 to 200 mg/kg, preferably 0.05 to 50 mg/kg, still preferably 0.1 to 10 mg/kg a day, and may be administered in a single dose or in divided doses, for example from 2 to 4 times a day.

The drug may be formulated into pharamceutical presentations using conventional formulation procedures. More specifically, a solid drug for oral application can be prepared by mixing an active principle with filler and, if necessary, binder, disintegrating agent, lubricant, coloring agent, corrigent or the like and converting the obtained mixture into a tablet, coated tablet, granule, powder or capsule.

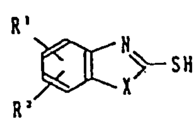
Examples of the filler include lactose, corn starch, sucrose, glucose, sorbitol, crystalline cellulose and silicon dioxide, while those of the binder include polyvinyl alcohol, polyvinyl ether, ethylcellulose, methylcellulose, acacia, tragacanth, gelatin, shellac, hydroxypropylcellulose, hydroxypropylstarch and polyvinylpyrrolidone. Examples of the disintegrating agent include starch, agar, gelatin powder, crystalline cellulose, calcium carbonate, sodium hydrogencarbonate, calcium citrate, dextrin and pectin, while those of the lubricant include magnesium stearate, talc, polyethylene glycol, silica and hardened vegatable oils. The coloring agent may be any one which is permitted to be added to drugs. Examples of the corrigent include cacao powder, mentha herb, aromatic powder, mentha oil, borneol and powdered cinnamon bark. Of course, these tablets and granules may be, if necessary, coated with sugar, gelatin or the like.

The injection can be prepared by mixing an active principle with pH adjusting agent, buffer, stabilizer, solubilizing agent or the like and treating the obtained mixture according to an ordinary process to obtain a subcutaneous, intramuscular or intravenous injection.

Preparation process

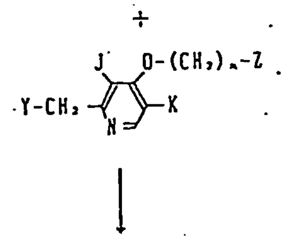
The compound of the present invention can be prepared by various processes, representative examples of which will now be described.

Preparation process A



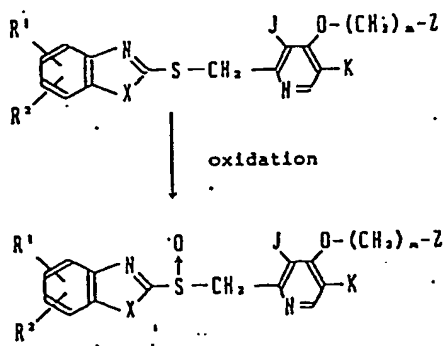
(II)

wherein R^1, R^2 and X are as defined above



(III)

wherein m, Z, J and K are as defined above and Y stands for a halogen atom or a sulfonyloxy group



(I')

oxidation

(I'')

That is, a compound represented by the general formula (II) is reacted with a halide or sulfonate represented by the general formula (III) to obtain a compound represented by the general formula (I') which is an objective compound of the present invention.

Examples of the halogen atom defined with respect to Y include chlorine, bromine and iodine, while those of the sulfonyloxy group include alkylsulfonyloxy groups such as methylsulfonyloxy and ethylsulfonyloxy groups and aromatic sulfonyloxy groups such as benzenesulfonyloxy and tosyloxy groups.

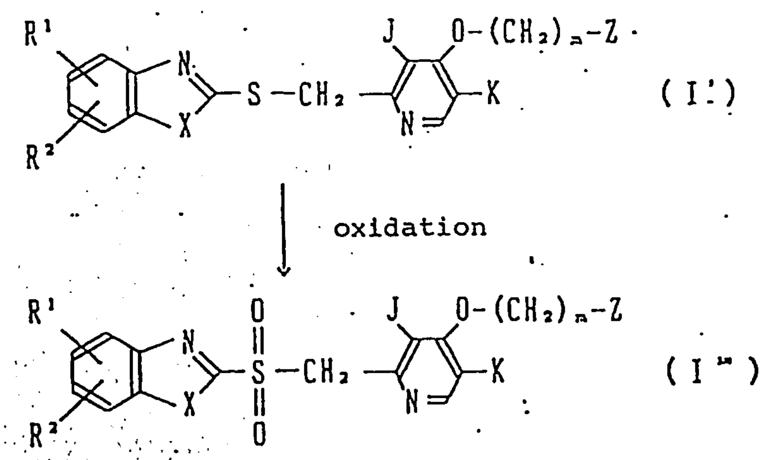
The above reaction is preferably carried out in the presence of an acid scavenger. Examples of the acid scavenger include carbonates and hydrocarbonates of alkali metals, such as potassium carbonate, sodium carbonate and sodium hydrogencarbonate; alkali hydroxides such as sodium hydroxide and potassium hydroxide and organic amines such as pyridine and triethylamine. Examples of the solvent to be used in the reaction include alcohols such as methyl and ethyl alcohols, tetrahydrofuran, dioxane, dimethylformamide, dimethyl sulfoxide and mixtures thereof with water.

The reaction temperature may be from -40°C to the boiling point of the solvent used, preferably from about 0 to 60°C.

The obtained compound (I') can be easily oxidized into its sulfinyl derivative (I'') which is an objective compound of the present invention corresponding to a compound of the general formula (I) wherein n is 1.

This oxidation can be carried out according to an ordinary process by the use of an oxidizing agent such as hydrogen peroxide, peracetic acid, m-chloroperbenzoic acid, sodium hypochlorite or sodium hypobromite. The solvent to be used in the oxidation is generally selected from among dichloromethane, chloroform, benzene, toluene, methanol, ethanol and the like. The oxidation temperature may be from -70°C to the boiling point of the solvent used, preferable from -60 to 25°C.

Furthermore, a sulfone derivative which is an objective compound of the present invention corresponding to a compound of the formula (I) wherein n is 2 can be prepared by, for example, the following process:



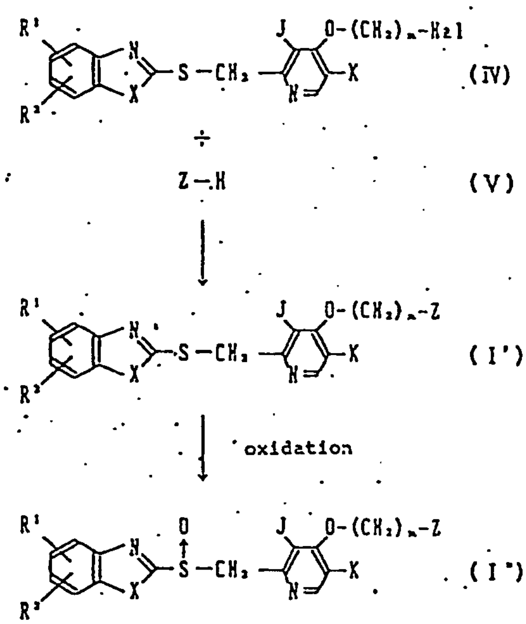
wherein R^1, R^2, X, J, m and Z are as defined above.

That is, the thio ether derivative represented by the general formula (I') which is an objective compound of the present invention is oxidized into its sulfone derivative represented by the general formula (I''') which is another objective compound of the present invention.

More precisely, the sulfone derivative (I''') which is an objective compound of the present invention can be prepared by dissolving the compound (I') in a solvent selected from among aromatic hydrocarbons such as benzene, toluene and xylene; halogenated hydrocarbons such as dichloromethane, chloroform and carbon tetrachloride; water; alcohols such as methanol and ethanol; ethyl acetate; acetone; acetic acid and the like to obtain a solution, adding at least twice by equivalent as much oxidizing agent selected from among hydrogen peroxide, peracetic acid, m-chloroperbenzoic acid, sodium hypochlorite, sodium m-periodate and the like to the solution under cooling with ice or at a room temperature and reacting the compound (I') with the oxidizing agent.

Alternatively, the sulfone derivative (I''') can be prepared by dissolving the sulfoxide derivative (I'') obtained by the above process in a solvent such as chloroform, adding an oxidizing agent such as m-chloroperbenzoic acid to the obtained solution and reacting the sulfoxide derivative (I'') with the oxidizing agent.

Preparation process B



wherein R^1, R^2, X, m, J, K and Z are as defined above and Hal stands for a halogen atom.

That is, an objective compound represented by the general formula (I) can be prepared by reacting a halide represented by the general formula (IV) with an alcohol, thiol or amine represented by the general formula: Z-H (V). This reaction is preferably carried out in the presence of an acid scavenger. Examples of the acid scavenger include carbonates and hydrogencarbonates of alkali metals, such as potassium carbonate and sodium carbonate; alkali hydroxides such as sodium hydroxide and potassium hydroxide and triethylamine. Examples of the solvent to be used in the reaction include ethers such as tetrahydrofuran and dioxane; ketones such as acetone and methyl ethyl ketone; benzene homologues such as benzene, toluene and xylene; acetonitrile; dimethylformamide; dimethyl sulfoxide and hexamethylphosphoric triamide. The reaction may be carried out either under cooling with ice or at a temperature not exceeding the boiling point of the solvent used.

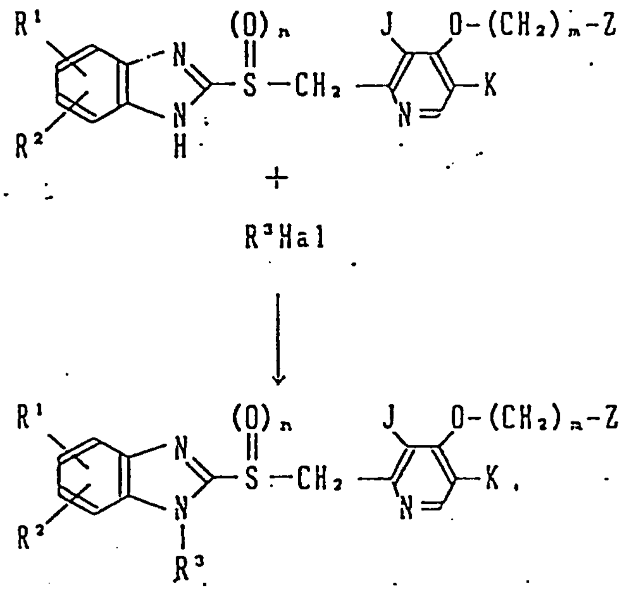
The obtained compound (I') which is an objective compound of the present invention can be oxidized into its sulfinyl derivative represented by the general formula (I") in a similar manner to that described above in Preparation process A.

Preparation process C

A compound represented by the general formula (I) wherein X is a group represented by the formula:

$$-\underset{R^3}{\underset{|}{N}}-$$

(wherein R^3 is a group selected from among those defined above except a hydrogen atom) can be prepared by the following process:



(VI)

(VII)

(I'''')

wherein R^1, R^2, n, J, K, m and Z are as defined above; Hal stands for a halogen atom and R^3 is a group selected from among those defined with respect to R^3 of the formula (I) except a hydrogen atom, i.e., a C_{1-6} alkyl, phenyl, benzyl or C_{1-6} alkoxycarbonyl group.

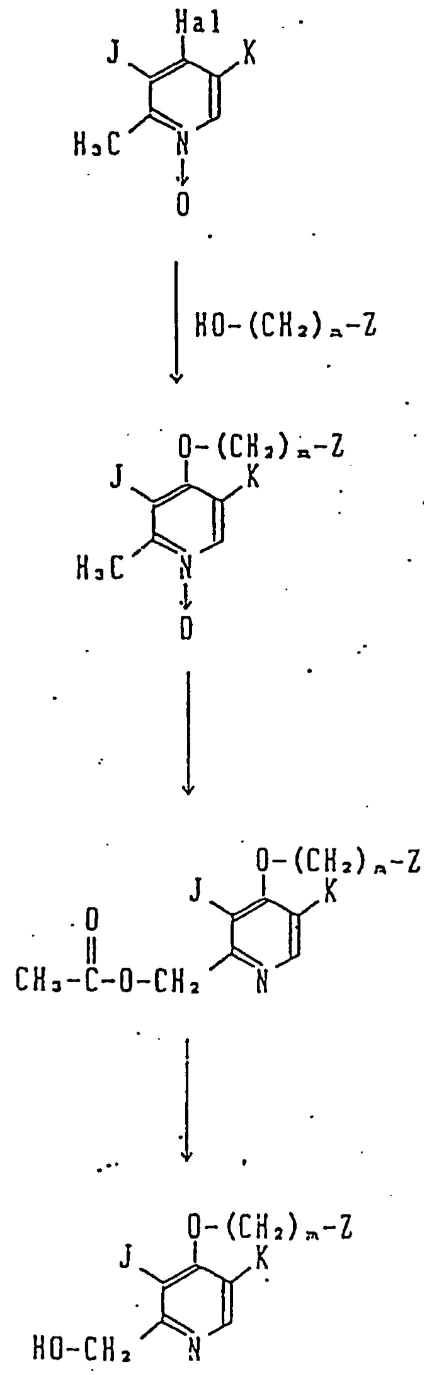
That is, a compound represented by the general formula (I'''') which is an objective compound of the present invention can be prepared by condensing a compound represented by the general formula (VI) with a halide represented by the general formula (VII) according to an ordinary process.

This condensation is carried out in the absence of any solvent or in an organic solvent inert to the condensation selected from among benzene, ethanol, xylene, tetrahydrofuran, chloroform, carbon tetrachloride, dimethylformamide and the like either at a room temperature or under cooling with ice or heating for several hours according to an ordinary process. The condensation can be expedited by the use of a dehydrohalogenating agent selected from among inorganic salts such as sodium hydrogencarbonate, potassium carbonate, sodium carbonate and caustic soda or organic bases such as triethylamine, pyridine, pyrimidine and diethylaniline.

Further, the thio ether derivative represented by the general formula (I''''), wherein n is 0, which has been prepared by condensing a compound represented by the general formula (VI), wherein n is 0, with a halide (VII) can be easily oxidized into the corresponding sulfoxide (n = 1) or sulfone (n = 2) derivative according to the same process as that described above.

Process for the preparation of starting materials

The compound represented by the general formula (III) to be used in the Preparation process A as a starting material can be prepared by, for example, the following process:



(VIII)

(Step 1)

(IX)

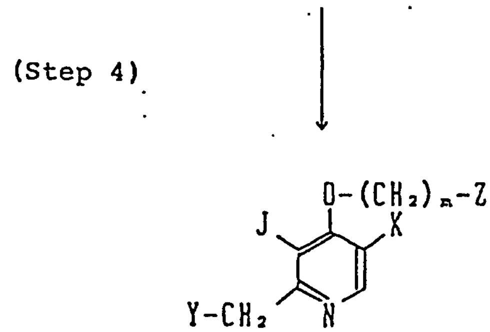
(X)

(Step 2)

(XI)

(Step 3)

(XII)



(III)

wherein m, Z, J, K and Y are as defined above.

(Step 1)

A 4-halogenopyridine oxide derivative (VIII) (for example, 4-chloro-2,3-dimethylpyridine 1-oxide) is reacted with an alcohol derivative represented by the general formula (IX) in the presence of a base to obtain an alkoxy derivative represented by the general formula (X).

Examples of the base include alkali metal hydrides such as sodium hydride and potassium hydride; alkali metals such as metallic sodium; sodium alcoholates such as sodium methoxide and alkali metal hydroxides such as sodium hydroxide and potassium hydroxide. This reaction is carried out either in the absence of any solvent or in a solvent selected from among ethers such as tetrahydrofuran and dioxane; ketones such as acetone and methyl ethyl ketone; benzene homologues such as benzene, toluene and xylene; acetonitrile; dimethylformamide; dimethyl sulfoxide; hexamethylphosphoric triamide and the like at a temperature of from one under cooling with ice to the boiling point of the solvent used.

(Step 2)

The alkoxy derivative of the general formula (X) prepared in the Step 1 is heated in acetic anhydride to a temperature of about 60 to 100°C to obtain an acetoxymethylpyridine derivative represented by the general formula (XI).

(Step 3)

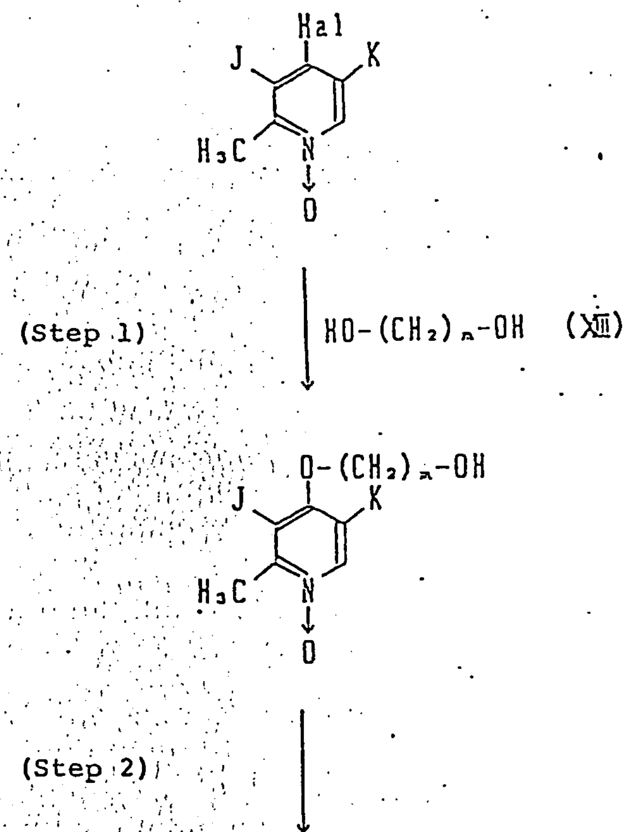
The acetoxymethylpyridine derivative (XI) prepared in the Step 2 is hydrolyzed into the corresponding 2-hydroxymethylpyridine derivative represetned by the general formula (XII).

This hydrolysis is generally carried out under alkaline conditions.

(Step 4)

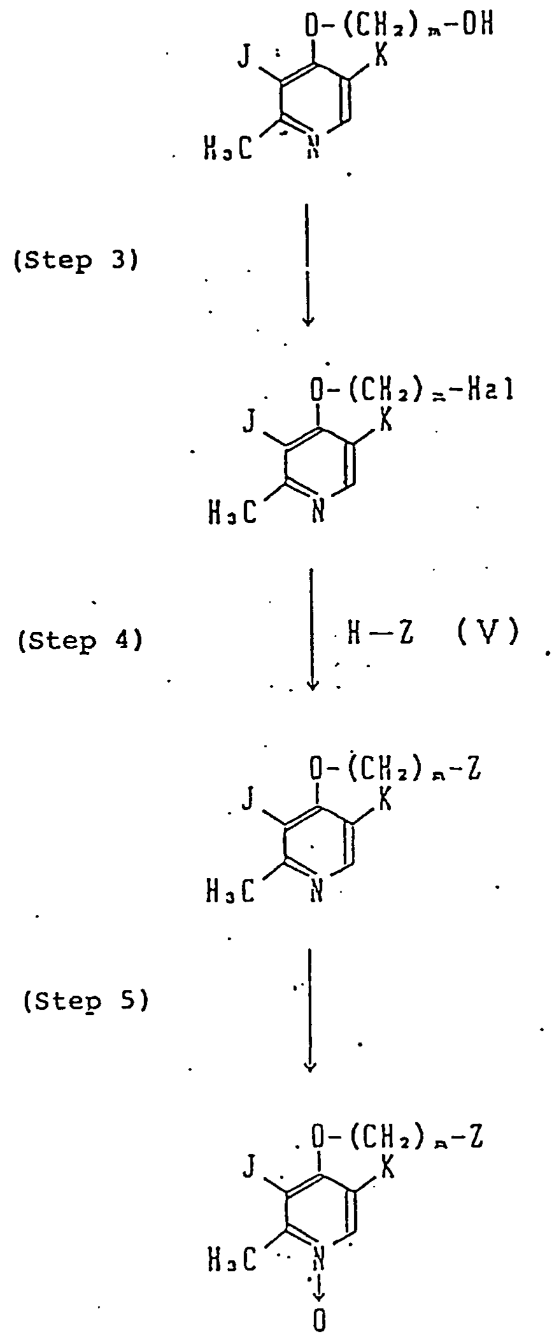
The 2-hydroxymethylpyridine derivative (XII) prepared in the Step 3 is halogenated with, for example, a chlorinating agent such as thionyl chloride into a 2-halogenomethylpyridine derivative represented by the general formula (III). In this halogenation, for example, chloroform or dichloromethane is used as a solvent. Further, the 2-hydroxymethylpyridine derivative (XII) is reacted with an active sulfonyl chloride such as methanesulfonyl chloride to obtain a sulfonyloxy derivative represented by the general formula (III). In this reaction, for example, chloroform, dichloromethane, ether, tetrahydrofuran, pyridine or benzene is used as a solvent.

Alternatively, the compound represented by the general formula (X) to be used in the above process can be prepared by the following process:



(VIII)

(XII')



(XV)

(XVI)

(XVII)

(X)

(Step 1)

A compound represented by the general formula (VIII), wherein Hal stands for a halogen atom such as chlorine atom, is condensed with a compound represented by the general formula (XIII) according to an ordinary process to

obtain a compound represented by the general formula (XIV).

This condensation is preferably carried out in the presence of a base selected from among alkali metal hydrides such as sodium hydride and potassium hydride; alkali netals such as metallic sodium; alkali metal hydroxides such as sodium hydroxide and potassium hydroxide and the like.

The condensation is carried out either in the absence of any solvent or in a solvent selected from among ethers such as tetrahydrofuran and dioxane; ketones such as acetone and methyl ethyl ketone; benzene homologues such as benzene, toluene and xylene; acetonitrile; dimethylformamide; dimethyl sulfoxide; hexamethylphosphoric triamide and the like at a temperature suitably selected from the range of one under cooling with ice to the boiling point of the solvent used.

(Step 2)

The obtained alkoxy derivative (XIV) is reduced into the compound (XV). Precisely, the alkoxy derivative (XIV) is hydrogenated in the presence of a 10% palladium/carbon catalyst in an acetic anhydride/acetic acid mixture to obtain the reduction product (XV).

(Step 3)

The obtained compound (XV) is halogenated with, for example, a chlorinating agent such as thionyl chloride to obtain a 2-halogenoethyl derivative represented by the general formula (XVI). In this halogenation, for example, chloroform or dichloromethane is used as a solvent.

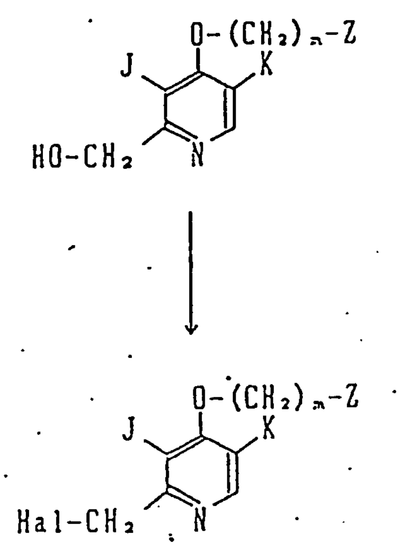
(Step 4)

The obtained compound (XVI) is reacted with an alcohol, thiol or amine represented by the general formula (V) to obtain a compound represented by the general formula (XVII). This reaction is preferably carried out in the presence of an acid scavenger as in the reaction of the Preparation process B.

(Step 5)

The obtained compound (XVII) is oxidized with an oxidizing agent such as hydrogen peroxide, peracetic acid or m-chloroperbenzoic acid to obtain the corresponding N-oxide derivative.

Alternatively, the compound represented by the general formula (III) to be used in the Preparation process A as a starting material can be prepared by the following process:



(XII)

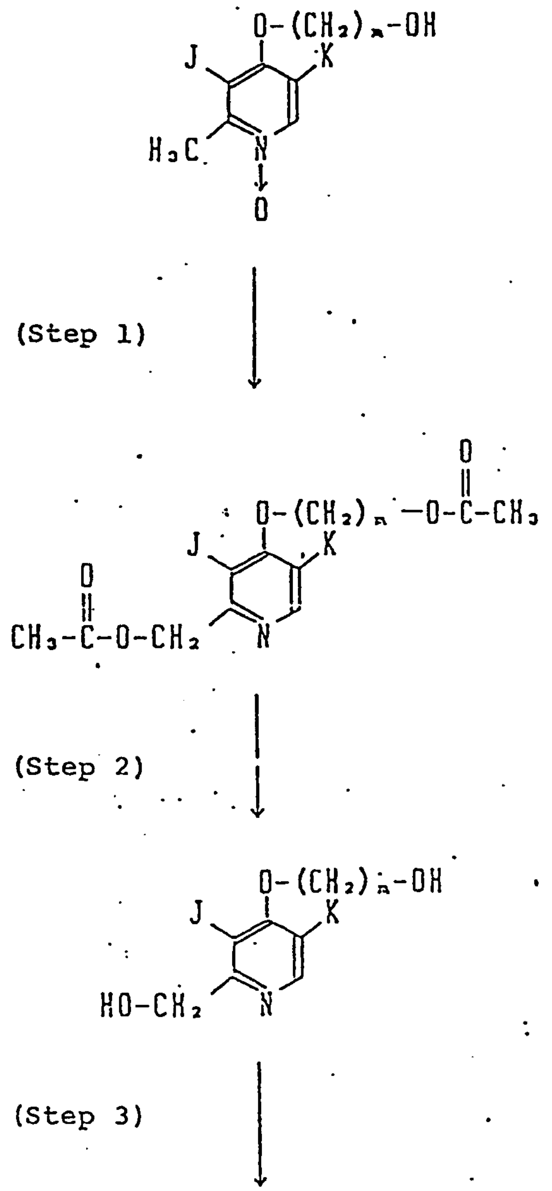
(III)

wherein Hal stands for a halogen atom and Z and m areas defined above.

A compound represented by the general formula (XII) is halogenated with, for example, a chlorinating agent such

as thionyl chloride at a temperature of 0°C to a room temperature to obtain a halogenomethylpyridine derivative represented by the general formula (III). In this halogenation, for example, chloroform or dichloromethane is used as a solvent.

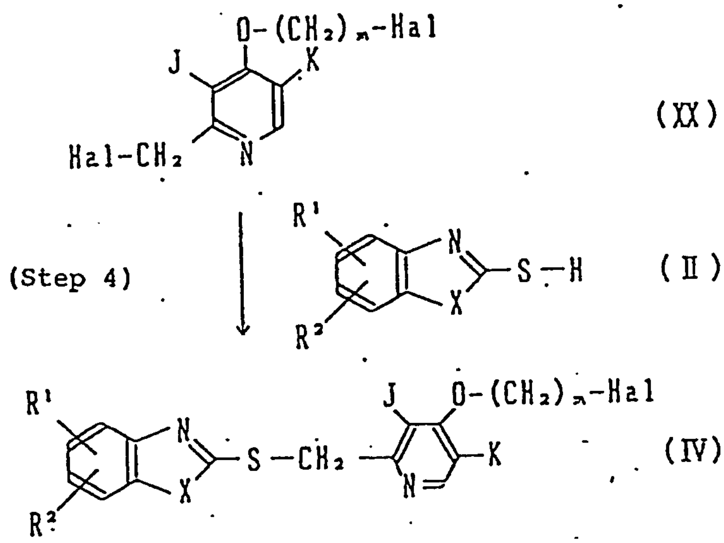
The compound (IV) to be used in the Preparation process B as a starting material can be prepared by, for example, the following process:



(XII)

(XIII)

(XIV)



wherein Hal stands for a halogen atom and the others are as defined above.

(Step 1)

A compound represented by the general formula (XIV) is converted into the corresponding acetylate (XVIII) according to an ordinary process. For example, acetic anhydride or acetyl chloride is used in this reaction.

(Step 2)

The obtained acetylate is hydrolyzed in the pressence of an acid or a base to obtain the corresponding diol derivative (XIX).

(Step 3)

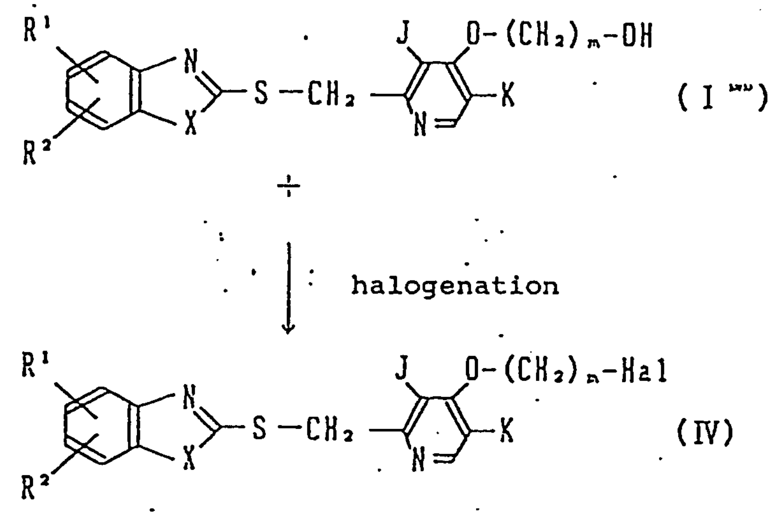
The diol derivative (XIX) is halogenated with, for example, a chlorinating agent such as thionyl chloride to obtain a dihalide represented by the general formula (XX). In this halogenation, for example, chloroform or dichloromethane is used as a solvent.

(Step 4)

The obtained dihalide (XX) is reacted with a compound represented by the general formula (II) to obtain a sulfide derivative represented by the general formula (IV).

This reaction is carried out in the presence of an acid scavenger selected from among carbonates and hydrogencarbonates of alkali metals, such as potassium carbonate and sodium carbonate, and alkali hydroxides such as sodium hydroxide and potassium hydroxide. Examples of the solvent to be used in the reaction include alcohols such as ethanol and methanol, tetrahydrofuran, dioxane, dimethylformamide, dimethyl sulfoxide and mixtures thereof with water. The reaction temperature may be from 0°C to the boiling point of the solvent used, preferably from about 40 to 60°C.

Alternatively, the compound (IV) to be used in the Preparation process B as a starting material can be prepared by the following process:



wherein Hal stands for a halogen atom and the others are as defined above.

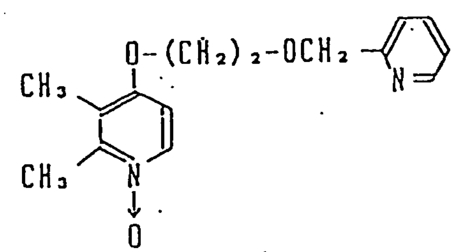
That is, the compound (IV) can be obtained by halogenating the compound (I''''') which is an objective compound of the present invention and prepared by the Preparation process A according to an ordinary process. More precisely, a compound represented by the general formula (I''''') is halogenated with, for example, a chlorinating agent such as thionyl chloride to obtain a halide represented by the general formula (IV). In this halogenation, chloroform or dichloromethane is preferably used as a solvent and the reaction temperature ranges preferably from a room temperature to about 80°C.

Examples of the present invention will now be described, though it is needless to say that the present invention is not limited by them at all.

The following Preparative Examples refer to the preparation of raw materials to be used in the preparation of the objective compounds according to the present invention.

Preparative Example 1

2,3-Dimethyl-4-(2-pyridylmethoxyethoxy)pyridine N-oxide

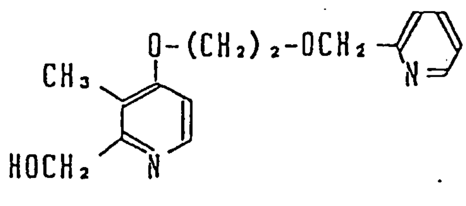


0.39 g of 60% sodium hydride was added to a suspension of 1.20 g (6.5 mmol) of 4-(2-hydroxyethoxy)-2,3-dimethylpyridine N-oxide in 40 ml of tetrahydrofuran under cooling with ice in a nitrogen atmosphere to obtain a mixture. This mixture was stirred for 0.5 hour, followed by the addition of 0.83 g (6.5 mmol) of 2-chloromethylpyridine. The obtained mixture was heated under reflux for 8 hours, cooled and filtered. The filtrate was concentrated and purified by silica gel column chromatography (solvent: ethyl acetate/n-hexane = 4 : 1 ~ $CHCl_3$/MeOH = 19 : 1) to obtain 0.61 g of 2,3-dimethyl-4-(2-pyridylmethoxyethoxy)pyridine N-oxide.

^1H-NMR($CDCl_3$) δ ;
2.20(s, 3H), 2.50(s, 3H), 3.80~4.04(m, 2H), 4.04~4.28(m, 2H), 4.70(s, 2H), 6.60(d, H), 7.00~7.74(m, 3H), 8.04(d, H), 8.45(d, H)

Preparative Example 2

2-Hydroxymethyl-3-methyl-4-(2-pyridylmethoxyethoxy)pyridine

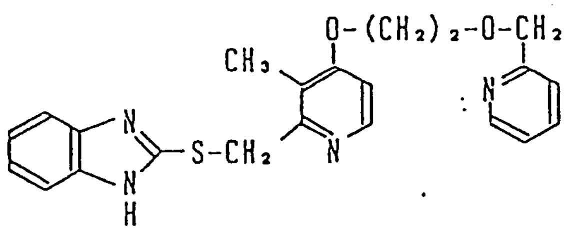


A mixture comprising 0.60 g of 2,3-dimethyl-4-(2-pyridylmethoxyethoxy)pyridine N-oxide and acetic anhydride was stirred at 100°C for 0.5 hour and cooled, followed by the addition of 40 ml of ethanol. The obtained mixture was stirred at a room temperature for 0.5 hour and distilled to remove the solvent. The residue was dried in a vacuum to obtain 0.47 g of crude 2-acetoxymethyl-3-methyl-4-(2-pyridylmethoxyethoxy)pyridine as an oil.

This crude intermediate was dissolved as such in 1 N HCl to obtain a solution. This solution was stirred at 100°C for one hour, cooled, neutralized with a saturated aqueous solution of sodium hydrogencarbonate and extracted with 50 ml of dichloromethane twice. The extract wad dried over magnesium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography (solvent: ehtyl acetate) to obtain 0.40 g of 2-hydroxymethyl-3-methyl-4-(2-pyridylmethoxyethoxy)pyridine as a colorless semicrystal.

Example 1

2-[{3-Methyl-4-(2-pyridylmethoxyethoxy)pyridine-2-yl}methylthio]-1H-benzimidazole



0.71 g (6 mmol) of thionyl chloride was added to a solution of 0.40 g (1.5 mmol) of 2-hhdroxymethyl-3-methyl-4-(2-pyridylmethoxyethoxy)pyridine in 10 ml of chloroform under cooling with ice to obtain a mixture. This mixture was stirred at 0°C for 2 hours. After the completion of the reaction, the mixture was neutralized with a saturated aqueous solution of sodium hydrogencarbonate and extracted with 50 ml of chloroform four times. The extract was dried over magnesium sulfate and filtered. The obtained filtrate was concentrated and dried in a vacuum to obtain 0.42 g of crude 2-chloromethyl-3-methyl-4-(2-pyridylmethoxyethoxy)pyridine as a semicrystal.

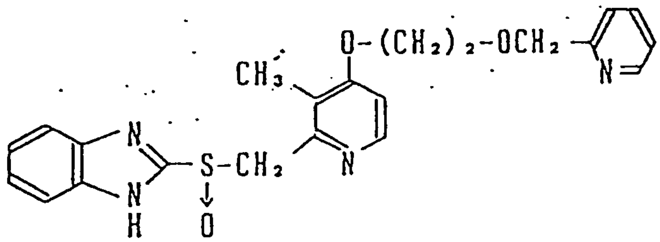
A mixture comprising 0.40 g of this crude intermediate, 0.18 g of 2-mercapto-1H-benzimidazole, 0.19 g of potassium carbonate and 30 ml of methyl ethyl ketone was heated under reflux in a nitrogen atmosphere for 2 hours, cooled and filtered. The filtrate was concentrated and purified by silica gel column chromatography (solvent: ethyl acetate/n-hexane) to obtain 0.38 g of 2-[{3-methyl-4-(2-pyridylmethoxyethoxy)pyridine-2-yl}methylthio]-1H-benzimidazole as a colorless oil.

^1H-NMR($CDCl_3$) δ ;
2.26 (s, 3H), 3.80~4.04(m, 2H), 4.10~4.28 (m, 2H), 4.35(s, 2H), 4.70(s, 2H), 6.70(d, H), 6.94~7.20(m, 7H), 8.25(d,

H), 8.45(d, H)

Example 2

2-[[3-Methyl-4-(2-pyridylmethoxyethoxy)pyridine-2-yl}methylfulfinyl]-1H-benzimidazole



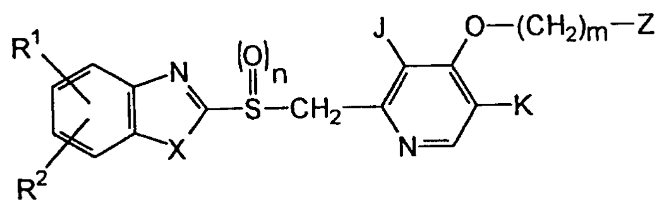
0.16 g of m-chloroperbenzoic acid was added to a solution of 0.38 g of 2-[{3-methyl-4-(2-pyridylmethoxyethoxy)pyridine-2-yl}methylthio]-1H-benzimidazole in 20 ml of dichloromethane at -60°C in a nitrogen atmosphere to obtain a mixture. This mixture was stirred for 0.5 hour. After the completion of the reaction, 0.16 g of triethylamine was added to the reaction mixture. The obtained mixture was heated to -10°C, followed by the addition of 30 ml of a saturated aqueous solution of sodium hydrogencarbonate. The obtained mixture was stirred at a room temperature for 0.5 hour and extracted with 50 ml of dichloromethane thrice. The extract was dried over magnesium sulfate and filtered. The filtrate was concentrated and dried in a vacuum to obtain a crude product. This crude product was crystallized from dichloromethane/diethyl ether to obtain 0.31 g of 2-[{3-methyl-4-(2-pyridylmethoxyethoxy)pyridine-2-yl}methylsulfinyl]-1H-benzimidazole as a white crystal.

^{1}H-NMR($CDCl_3$) δ ;
2.17(s, 3H), 3.83~4.06(m, 2H), 4.06~4.34 (m, 2H), 4.72(s, 2H), 4.64~4.84(m, 2H), 6.70(d, H), 7.04~7.80(m, 7H), 8.27(d, H), 8.55(d, H)

Claims

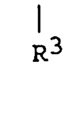
Claims for the following Contracting States : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. A pyridine derivative represented by the general formula (I):



(I)

wherein R^1 and R^2 may be the same or different from each other and each stand for a hydrogen atom, a C_{1-6} alkyl, C_{1-6} alkoxy, halogenated C_{1-6} alkyl, (C_{1-6} alkoxy)carbonyl or carboxyl group or a halogen atom;
X stands for a group represented by the formula: -O-, -S- or



(wherein R^3 stands for a hydrogen atom or a C_{1-6} alkyl, phenyl, benzyl or (C_{1-6} alkoxy)carbonyl group);

Z stands for
a group represented by the general formula:

$$-O-(CH_2)_q-R^5$$

wherein q stands for an integer of 1 to 3 and R^5 stands for a naphthyl group, which may be substituted with a C_{1-6} alkoxy group, a hydroxyl group or a halogen atom; a pyridyl group or a furyl group,

n stands for an integer of 0 to 2; m stands for an integer of 2 to 10; and

J and K may be the same or different from each other and each stand for a hydrogen atom or a C_{1-6} alkyl group, and a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein R^5 represents a pyridyl group or a furyl group.

3. A compound according to claim 2, wherein R^5 represents a pyridyl group.

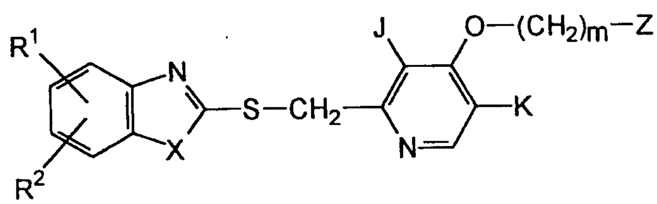
4. A pharmaceutical composition which comprises a pharmacologically effective amount of a pyridine derivative according to any of the claims 1 to 3 or a pharmacologically acceptable salt thereof and a pharmacologically acceptable carrier.

5. A pharmaceutical composition according to claim 4 which comprises 0.1 to 100 g of the pyridine derivative or a pharmacologically acceptable salt thereof per unit dose.

6. A pharmaceutical composition according to claim 4 or 5 for the treatment or prevention of peptic ulcers.

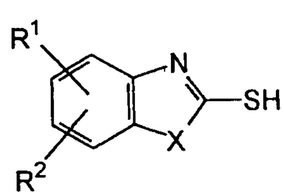
7. The use of a pyridine derivative according to any of the claims 1 to 3 for the manufacture of a medicament for the treatment or prevention of peptic ulcers.

8. A process for producing a compound of general formula I':



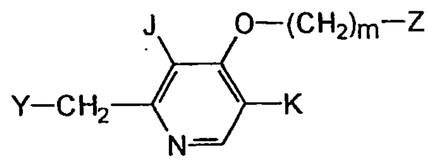
(I')

wherein R^1, R^2, X, J, K, Z and m are as defined in claim 1,
or a pharmaceutically acceptable salt thereof,
comprising the step of reacting the compound of formula II with the compound of formula III



(II)

wherein R^1, R^2 and X are as defined above



(III)

wherein m, Z, J and K are as defined above and Y represents a halogen atom or a sulfonyloxy group, and optionally converting the product into a salt.

9. A process according to claim 8, wherein Y represents chlorine, bromine or iodine.

10. A process according to claim 8, wherein Y represents an alkyl sulfonyloxy group.

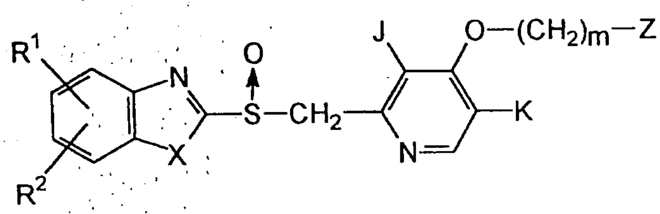
11. A process according to claim 10, wherein the alkyl sulfonyloxy group is a methyl sulfonyloxy group or an ethyl sulfonyloxy group.

12. A process according to claim 10, wherein the sulfonyloxy group is an aromatic sulfonyloxy group.

13. A process according to claim 12, wherein the aromatic sulfonyloxy group is a benzene sulfonyloxy group or a tosyloxy group.

14. A process according to any of claims 8 to 13, wherein the reaction is carried out in the presence of an acid scavenger.

15. A process for producing a compound of formula I":

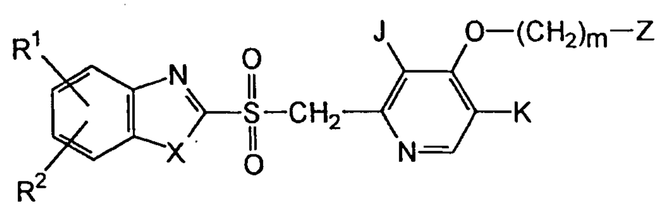


(I")

wherein R^1, R^2, X, J, K, Z and m are as defined in claim 1,
or a pharmaceutically acceptable salt thereof,
comprising the step of reacting the compound of formula I' as defined in claim 8 with an approximately equimolar amount of an oxidizing agent, and optionally converting the product into a salt.

16. A process according to claim 15, wherein the oxidizing agent is selected from hydrogen peroxide, peracetic acid, m-chloroperbenzoic acid, sodium hypochlorite or sodium hypobromite.

17. A process for producing a compound of formula I''':

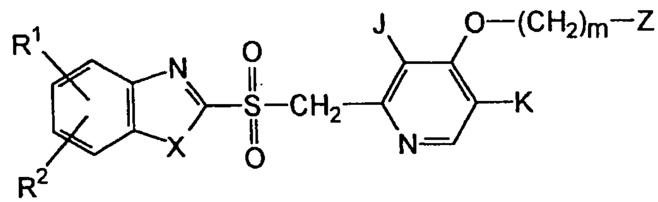


(I''')

wherein R^1, R^2, X, J, K, Z and m are as defined in claim 1, or a pharmaceutically acceptable salt thereof, comprising the step of reacting the compound of formula I' as defined in claim 8 with at least two molar equivalent amounts of an oxidizing agent, and optionally converting the product into a salt.

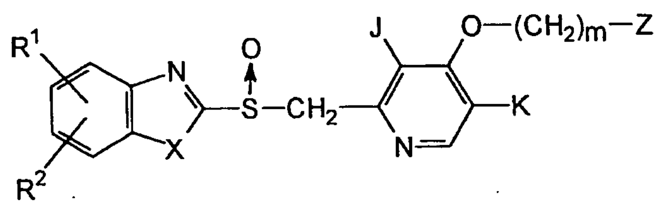
18. A process according to claim 17, wherein the oxidizing agent is selected from hydrogen peroxide, peracetic acid, m-chloroperbenzoic acid, sodium hypochlorite or sodium m-periodate.

19. A process for producing the compound of formula I''':



(I''')

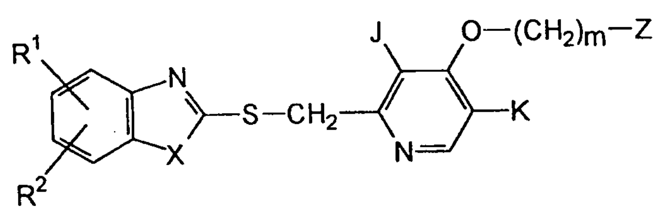
wherein R^1, R^2, X, J, K, Z and m are as defined in claim 1, or a pharmaceutically acceptable salt thereof, comprising the step of reacting an oxidising agent with a compound of formula I'':



(I'')

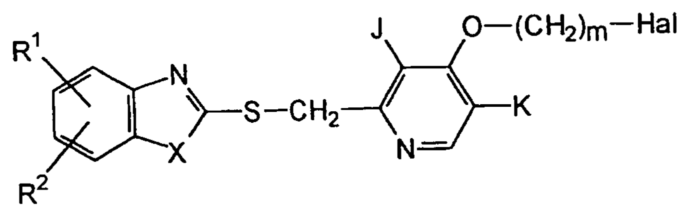
wherein R^1, R^2, X, J, K, Z and m are as defined above, and optionally converting the product into a salt.

20. A process for producing a compound of formula I':



(I')

wherein R^1, R^2, X, J, K, Z and m are as defined in claim 1, or a pharmaceutically acceptable salt thereof, comprising the step of reacting a compound of formula IV:

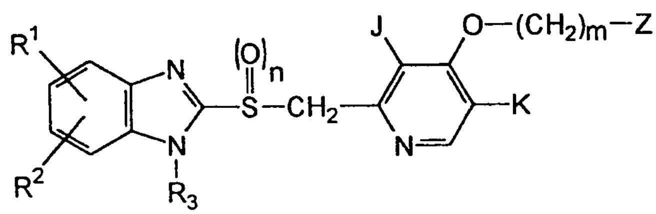


(IV)

wherein R^1, R^2, X, K, J and m are as defined above and Hal represents a halogen atom, with a compound of formula Z-H, wherein Z is as defined above, and optionally converting the product into a salt.

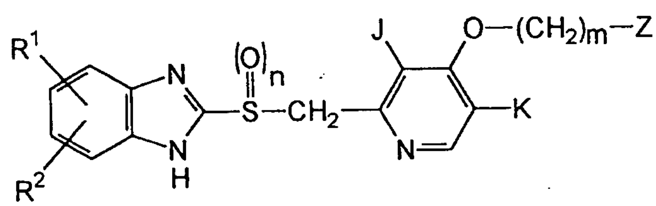
21. A process according to claim 20, wherein the reaction is carried out in the presence of an acid scavenger.

22. A process for producing a compound of formula I'''':



(I'''')

wherein R^1, R^2, n, J, K, m and Z are as defined in claim 1 and R^3 represents a C_{1-6} alkyl, phenyl, benzyl or (C_{1-6} alkoxy)carbonyl group, or a pharmaceutically acceptable salt thereof, comprising the step of reacting the compound of formula VI:



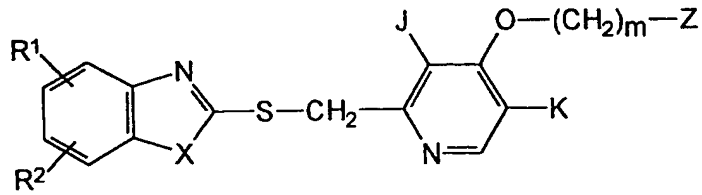
(VI)

wherein R^1, R^2, n, J, K, m and Z are as defined above, with R^3Hal, wherein Hal represents a halogen atom, and optionally converting the product into a salt.

23. A process according to claim 22, which is carried out in the presence of a dehydrohalogenating agent.

Claims for the following Contracting States : ES, GR

1. A process for producing a pyridine derivative represented by the general formula I':



(I')

wherein R^1 and R^2 may be the same or different from each other and each stand for a hydrogen atom, a C_{1-6} alkyl, C_{1-6} alkoxy, halogenated C_{1-6} alkyl, (C_{1-6} alkoxy)carbonyl or carboxyl group or a halogen atom; X stands for a group represented by the formula: -O-, -S- or

$$-\underset{\underset{R^3}{|}}{N}-$$

(wherein R^3 stands for a hydrogen atom or a C_{1-6} alkyl, phenyl, benzyl or (C_{1-6} alkoxy)carbonyl group);

Z stands for
a group represented by the general formula:

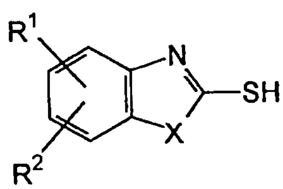
$$-O-(CH_2)_q-R^5$$

wherein q stands for an integer of 1 to 3 and R^5 stands for a naphthyl group, which may be substituted with a C_{1-6} alkoxy group, a hydroxyl group or a halogen atom; a pyridyl group or a furyl group,

m stands for an integer of 2 to 10; and

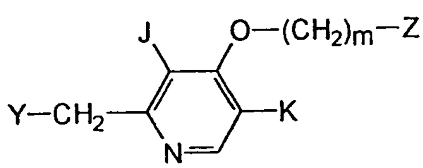
J and K may be the same or different from each other and each stand for a hydrogen atom or a C_{1-6} alkyl group, and a pharmaceutically acceptable salt thereof,

comprising the step of reacting the compound of formula II with the compound of formula III



(II).

wherein R^1, R^2 and X are as defined above



(III)

wherein m, Z, J and K are as defined above and Y represents a halogen atom or a sulfonyloxy group,

and optionally converting the product into a salt.

2. A process according to claim 1, wherein Y represents chlorine, bromine or iodine.

3. A process according to claim 1, wherein Y represents an alkyl sulfonyloxy group.

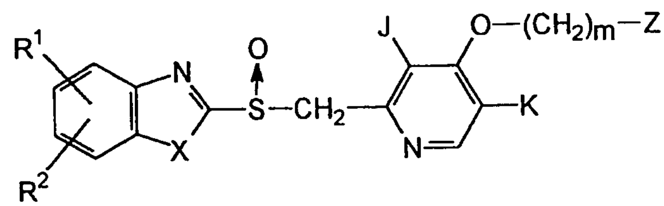
4. A process according to claim 3, wherein the alkyl sulfonyloxy group is a methyl sulfonyloxy group or an ethyl sulfonyloxy group.

5. A process according to claim 3, wherein the sulfonyloxy group is an aromatic sulfonyloxy group.

6. A process according to claim 5, wherein the aromatic sulfonyloxy group is a benzene sulfonyloxy group or a tosyloxy group.

7. A process according to any of claims 1 to 6, wherein the reaction is carried out in the presence of an acid scavenger.

8. A process for producing a compound of formula I":

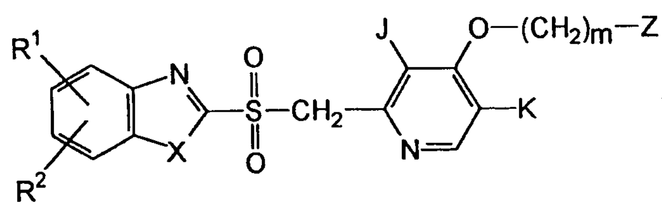


(I")

wherein R^1, R^2, X, J, K, Z and m are as defined in claim 1,
or a pharmaceutically acceptable salt thereof,
comprising the step of reacting the compound of formula I' as defined in claim 1 with an approximately equimolar amount of an oxidizing agent, and optionally converting the product into a salt.

9. A process according to claim 8, wherein the oxidizing agent is selected from hydrogen peroxide, peracetic acid, m-chloroperbenzoic acid, sodium hypochlorite or sodium hypobromite.

10. A process for producing a compound of formula I''':

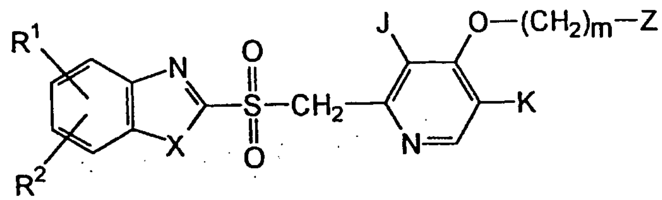


(I''')

wherein R^1, R^2, X, J, K, Z and m are as defined in claim 1,
or a pharmaceutically acceptable salt thereof,
comprising the step of reacting the compound of formula I' as defined in claim 1 with at least two molar equivalent amounts of an oxidizing agent, and optionally convering the product into a salt.

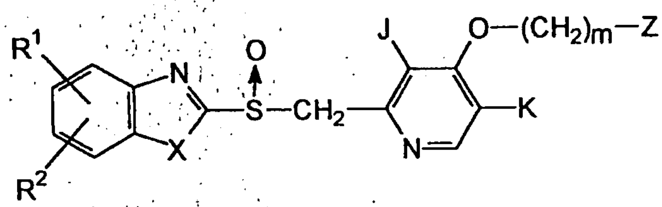
11. A process according to claim 10, wherein the oxidizing agent is selected from hydrogen peroxide, peracetic acid, m-chloroperbenzoic acid, sodium hypochlorite or sodium m-periodate.

12. A process for producing the compound of formula I''':



(I''')

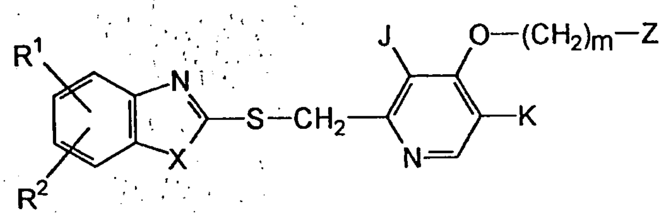
wherein R^1, R^2, X, J, K, Z and m are as defined in claim 1, or a pharmaceutically acceptable salt thereof, comprising the step of reacting an oxidizing agent with a compound of formula I":



(I")

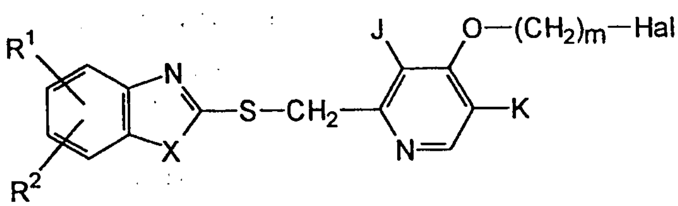
wherein R^1, R^2, X, J, K, Z and m are as defined above, and optionally converting the product into a salt.

13. A process for producing a compound of formula I':



(I')

wherein R^1, R^2, X, J, K, Z and m are as defined in claim 1, or a pharmaceutically acceptable salt thereof, comprising the step of reacting a compound of formula IV:

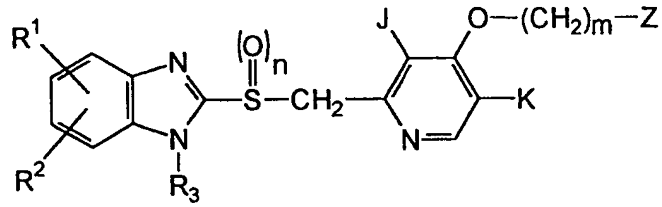


(IV)

wherein R^1, R^2, X, K, J and m are as defined above and Hal represents a halogen atom, with a compound of formula Z-H, wherein Z is as defined above, and optionally converting the product into a salt.

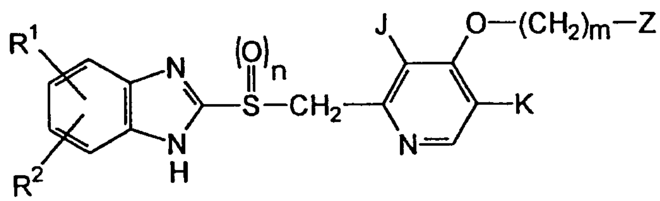
14. A process according to claim 13, wherein the reaction is carried out in the presence of an acid scavenger.

15. A process for producing a compound of formula I'''':



(I'''')

wherein R^1, R^2, J, K, m and Z are as defined in claim 1 and R^3 represents a C_{1-6} alkyl, phenyl, benzyl or (C_{1-6} alkoxy)carbonyl group, n stands for an integer from 0 to 2, or a pharmaceutically acceptable salt thereof, comprising the step of reacting the compound of formula VI:



(VI)

wherein R^1, R^2, n, J, K, m and Z are as defined above, with R^3Hal, wherein Hal represents a halogen atom, and optionally converting the product into a salt.

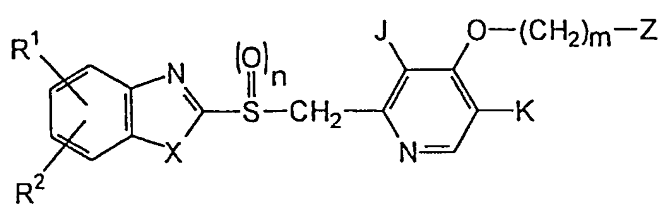
16. A process according to claim 15, which is carried out in the presence of a dehydrohalogenating agent.

17. The process of preparing a pharmaceutical composition for the treatment or prevention of peptic ulcers which comprises formulating 0.1 to 100 g of the pyridine derivative or a pharmacologically acceptable salt thereof per unit dose obtained by a process according to any of the foregoing claims together with a pharmacologically acceptable carrier.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Pyridinderivat der allgemeinen Formel I



(I)

worin R^1 und R^2 gleich oder verschieden sein können und ein Wasserstoffatom, ein C_1-C_6-Alkyl, C_1-C_6-Alkoxy, halogeniertes C_1-C_6-Alkyl, (C_1-C_6-Alkoxy)carbonyl oder Carboxyl oder ein Halogenatom bedeuten; X eine Gruppe bedeutet, dargestellt durch die Formel: -O-, -S- oder

(worin R^3 ein Wasserstoffatom oder C_1-C_6-Alkyl, Phenyl, Benzyl oder (C_1-C_6-Alkoxy)carbonyl bedeutet);

Z eine Gruppe der allgemeinen Formel:

$$-O-(CH_2)_q-R^5$$

worin q eine ganze Zahl von 1 bis 3 ist, und R^5 eine Naphthylgruppe, die mit einer C_1-C_6-Alkoxygruppe, eine Hydroxylgruppe oder einem Halogenatom substituiert sein kann; eine Pyridylgruppe oder eine Furylgruppe bedeutet,
n eine ganze Zahl von 0 bis 2 bedeutet; m eine ganze Zahl von 2 bis 10 bedeutet; und
J und K gleich oder verschieden sein können und ein Wasserstoffatom oder eine C_1-C_6-Alkylgruppe bedeuten,
und ein pharmazeutisch annehmbares Salz davon.

2. Verbindung nach Anspruch 1, dadurch gekennzeichnet, daß R^5 eine Pyridylgruppe oder eine Furylgruppe ist.

3. Verbindung nach Anspruch 2, dadurch gekennzeichnet, daß R^5 eine Pyridylgruppe ist.

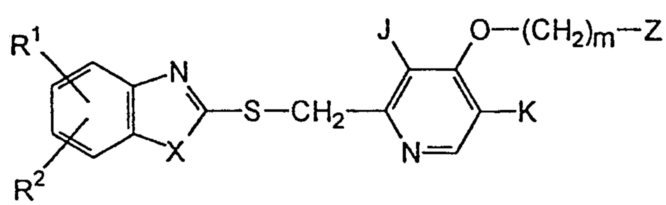
4. Pharmazeutische Zusammensetzung umfassend eine pharmakologisch wirksame Menge eines Pyridinderivats nach einem der Ansprüche 1 bis 3 oder ein pharmakologisch annehmbares Salz davon und einen pharmakologisch annehmbaren Träger.

5. Pharmazeutische Zusammmensetzung nach Anspruch 4, dadurch gekennzeichnet, daß sie pro Dosierungseinheit 0,1 bis 100 g des Pyridinderivats oder eines pharmakologisch annehmbaren Salzes davon umfaßt.

6. Pharmazeutische Zusammensetzung nach Anspruch 4 oder 5 zur Behandlung oder Vorbeugung von Magengeschwüren.

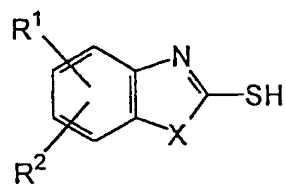
7. Verwendung eines Pyridinderivats nach einem der Ansprüche 1 bis 3 zur Herstellung eines Arzneimittels zur Behandlung oder Vorbeugung von Magengeschwüren.

8. Verfahren zur Herstellung einer Verbindung der allgemeinen Formel I':



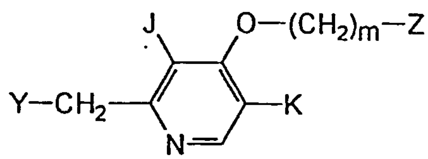
(I')

worin R^1, R^2, X, J, K, Z und m die im Anspruch 1 angegebene Bedeutung besitzen, oder einem pharmazeutisch annehmbaren Salz davon, umfassend die Stufe der Umsetzung der Verbindung der Formel II mit der Verbindung der Formel III



(II)

worin R^1, R^2 und X die vorstehend angegebene Bedeutung besitzen,



(III)

worin m, Z, J und K die vorstehend angegebene Bedeutung besitzen und Y ein Halogenatom oder eine Sulfonyloxygruppe bedeutet, und gegebenenfalls die Überführung des Produkts in ein Salz.

9. Verfahren nach Anspruch 8, dadurch gekennzeichnet, daß Y Chlor, Brom oder Jod bedeutet.

10. Verfahren nach Anspruch 8, dadurch gekennzeichnet, daß Y eine Alkylsulfonyloxygruppe bedeutet.

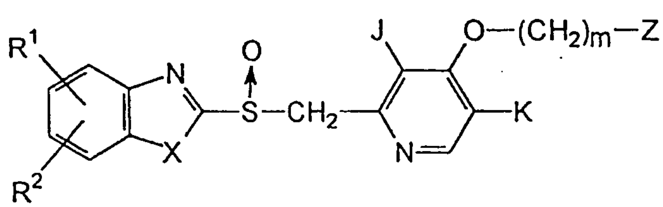
11. Verfahren nach Anspruch 10, dadurch gekennzeichnet, daß die Alkylsulfonyloxygruppe eine Methylsulfonyloxygruppe oder eine Ethylsulfonyloxygruppe ist.

12. Verfahren nach Anspruch 10, dadurch gekennzeichnet, daß die Sulfonyloxygruppe eine aromatische Sulfonyloxygruppe ist.

13. Verfahren nach Anspruch 12, dadurch gekennzeichnet, daß die aromatische Sulfonyloxygruppe eine Benzolsulfonyloxygruppe oder eine Tosyloxygruppe ist.

14. Verfahren nach einem der Ansprüche 8 bis 13, dadurch gekennzeichnet, daß die Umsetzung in Gegenwart eines Säure-abfangenden Mittels durchgeführt wird.

15. Verfahren zur Herstellung einer Verbindung der Formel I":

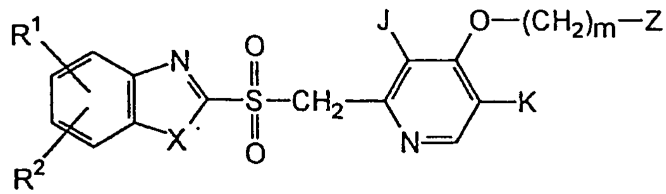


(I")

worin R^1, R^2, X, J, K, Z und m die in Anspruch 1 angegebene Bedeutung besitzen, oder eines pharmazeutisch annehmbaren Salzes davon, umfassend die Stufe der Umsetzung der Verbindung der Formel I' nach Anspruch 8 mit einer ungefähr äquimolaren Menge eines Oxidationsmittels, und gegebenenfalls die Überführung des Produkts in ein Salz.

16. Verfahren nach Anspruch 15, dadurch gekennzeichnet, daß das Oxidationsmittel ausgewählt ist aus Wasserstoffperoxid, Peressigsäure, m-Chlorperbenzoesäure, Natriumhypochlorit oder Natriumhypobromit.

17. Verfahren zur Herstellung einer Verbindung der Formel I''':

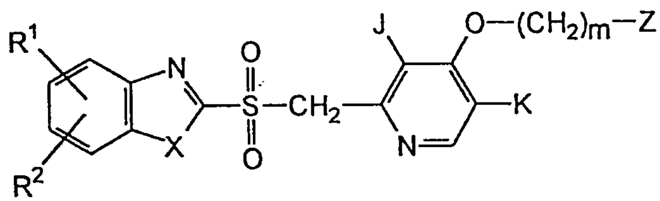


(I''')

worin R^1, R^2, X, J, K, Z und m die im Anspruch 1 angegebene Bedeutung besitzen, oder einem pharmazeutisch annehmbaren Salz davon, umfassend die Stufe der Umsetzung der Verbindung der Formel I' nach Anspruch 8 mit mindestens zwei Moläquivalenten eines Oxidationsmittels und gegebenenfalls die Überführung des Produkts in ein Salz.

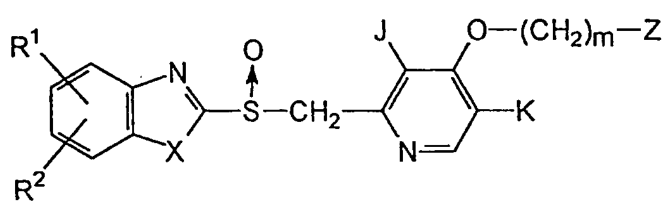
18. Verfahren nach Anspruch 17, dadurch gekennzeichnet, daß das Oxidationsmittel ausgewählt ist aus Wasserstoffperoxid, Peressigsäure, m-Chlorperbenzoesäure, Natriumhypochlorit oder Natrium-m-perjodat.

19. Verfahren zur Herstellung einer Verbindung der Formel I''':



(I''')

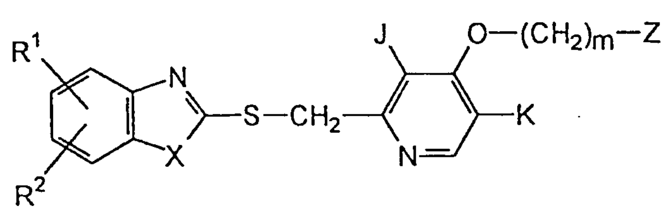
worin R^1, R^2, X, J, K, Z und m die im Anspruch 1 angegebene Bedeutung besitzen, oder einem pharmazeutisch annehmbaren Salz davon,
umfassend die Stufe der Umsetzung eines Oxidationsmittels mit einer Verbindung der Formel I'':



(I'')

worin R^1, R^2, X, J, K, Z und m die vorstehend angegebene Bedeutung besitzen, und gegebenenfalls die Überführung des Produkts in ein Salz.

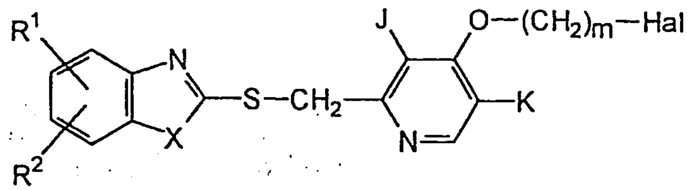
20. Verfahren zur Herstellung einer Verbindung der Formel I':



(I')

worin R^1, R^2, X, J, K, Z und m die in Anspruch 1 angegebene Bedeutung besitzen, oder einem pharmazeutisch

annehmbaren Salz davon,
umfassend die Stufe der Umsetzung einer Verbindung der Formel IV:

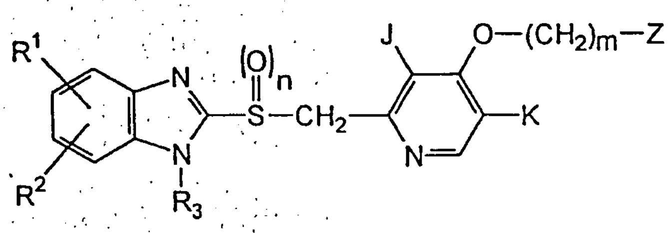


(IV)

worin R^1, R^2, X, K, J und m die vorstehend angegebene Bedeutung besitzen und Hal ein Halogenatom bedeutet, mit einer Verbindung der Formel Z-H, worin Z die vorstehend angegebene Bedeutung besitzt, und gegebenenfalls die Überführung des Produkts in ein Salz.

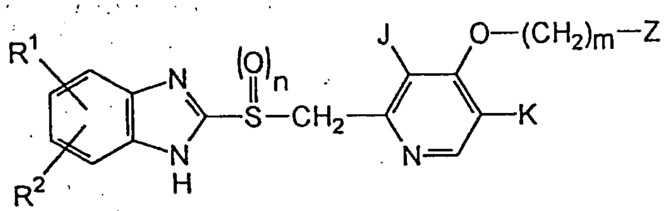
21. Verfahren nach Anspruch 20, dadurch gekennzeichnet, daß die Umsetzung in Gegenwart eines Säure-abfangenden Mittels durchgeführt wird.

22. Verfahren zur Herstellung einer Verbindung der Formel I'''':



(I'''')

worin R^1, R^2, n, J, K, m und Z die im Anspruch 1 angegebene Bedeutung besitzen und R^3 ein C_1-C_6-Alkyl, Phenyl, Benzyl oder eine (C_1-C_6-Alkoxy)carbonylgruppe bedeutet, oder einem pharmazeutisch annehmbaren Salz davon, umfassend die Stufe der Umsetzung der Verbindung der Formel VI



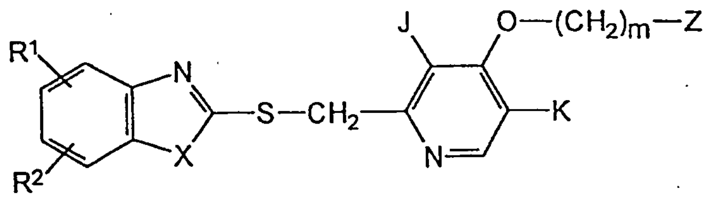
(VI)

worin R^1, R^2, n, J, K, m und Z die vorstehend angegebene Bedeutung besitzen, mit R^3Hal, worin Hal ein Halogenatom bedeutet, und gegebenenfalls die Überführung des Produkts in ein Salz.

23. Verfahren nach Anspruch 22, dadurch gekennzeichnet, daß es in Gegenwart eines Dehydrohalogenierungsmittels durchgeführt wird.

Patentansprüche für folgende Vertragsstaaten : ES, GR

1. Verfahren zur Herstellung eines Pyridinderivats der allgemeinen Formel I':



(I')

worin R^1 und R^2 gleich oder verschieden sein können und ein Wasserstoffatom, C_1-C_6-Alkyl, C_1-C_6-Alkoxy, halogeniertes C_1-C_6-Alkyl, (C_1-C_6-Alkoxy)carbonyl- oder Carboxyl oder ein Halogenatom bedeuten; X eine Gruppe bedeutet, dargestellt durch die Formel: -O-, -S- oder

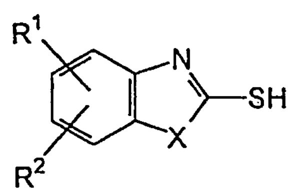
(worin R^3 ein Wasserstoffatom oder C_1-C_6-Alkyl, Phenyl, Benzyl oder (C_1-C_6-Alkoxy)carbonyl bedeutet;

Z eine Gruppe der allgemeinen Formel:

$$-O-(CH_2)_q-R^5$$

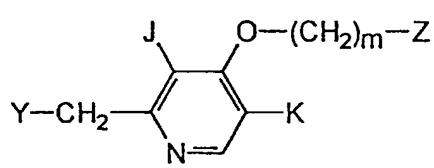
worin q eine ganze zahl von 1 bis 3 ist, und R^5 eine Naphthylgruppe, die mit einer C_1-C_6-Alkoxygruppe, einer Hydroxylgruppe oder einem Halogenatom substituiert sein kann; eine Pyridylgruppe oder eine Furylgruppe bedeutet,
n eine ganze Zahl von 0 bis 2 ist; m eine ganze Zahl von 2 bis 10 bedeutet; und
J und K gleich oder verschieden sein können und ein Wasserstoffatom oder eine C_1-C_6-Alkylgruppe bedeuten, und ein pharmazeutisch annehmbares Salz davon,

umfassend die Stufe der Umsetzung der Verbindung der Formel II mit der Verbindung der Formel III



(II)

worin R^1, R^2 und X die vorstehend angegebene Bedeutung besitzen,



(III)

worin m, Z, J und K die vorstehend angegebene Bedeutung besitzen und Y ein Halogenatom oder eine Sulfonyloxygruppe bedeutet, und
gegebenenfalls die Überführung eines Produkts in ein Salz.

2. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß Y Chlor, Brom oder Jod ist.

3. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß Y eine Alkylsulfonyloxygruppe ist.

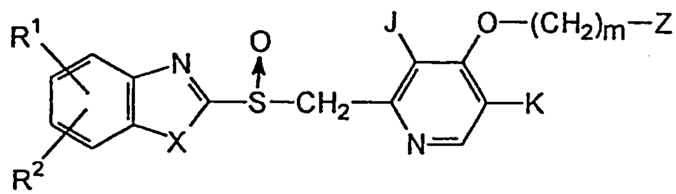
4. Verfahren nach Anspruch 3, dadurch gekennzeichnet, daß die Alkylsulfonyloxygruppe eine Methylsulfonyloxygruppe oder eine Ethylsulfonyloxygruppe ist.

5. Verfahren nach Anspruch 3, dadurch gekennzeichnet, daß die Sulfonyloxygruppe eine aromatische Sulfonyloxygruppe ist.

6. Verfahren nach Anspruch 5, dadurch gekennzeichnet, daß die aromatische Sulfonyloxygruppe eine Benzolsulfonyloxygruppe oder eine Tosyloxygruppe ist.

7. Verfahren nach einem der Ansprüche 1 bis 6, dadurch gekennzeichnet, daß die Umsetzung in Gegenwart eines Säure-abfangenden Mittels durchgeführt wird.

8. Verfahren zur Herstellung einer Verbindung der Formel I":

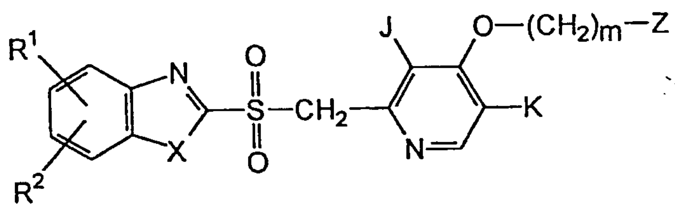


(I")

worin R^1, R^2, X, J, K, Z und m die in Anspruch 1 angegebene Bedeutung besitzen, oder eines pharmazeutisch annehmbaren Salzes davon, umfassend die Stufe der Umsetzung der Verbindung der Formel I' nach Anspruch 1 mit einer ungefähr äquimolaren Menge eines Oxidationsmittels, und gegebenenfalls die Überführung des Produkts in ein Salz.

9. Verfahren nach Anspruch 8, dadurch gekennzeichnet, daß das Oxidationsmittel ausgewählt ist aus Wasserstoffperoxid, Peressigsäure, m-Chlorperbenzoesäure, Natriumhypochlorit oder Natriumhypobromit.

10. Verfahren zur Herstellung einer Verbindung der Formel I''':

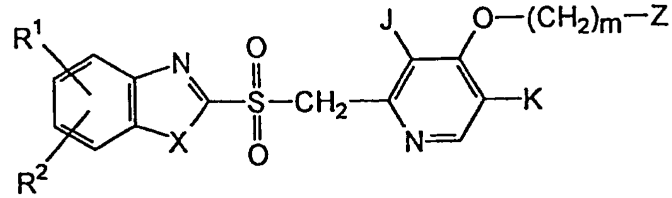


(I''')

worin R^1, R^2, X, J, K, Z und m die im Anspruch 1 angegebene Bedeutung besitzen, oder einem pharmazeutisch annehmbaren Salz davon,
umfassend die Stufe der Umsetzung der Verbindung der Formel I' nach Anspruch 1 mit mindestens zwei Moläquivalenten eines Oxidationsmittels, und gegebenenfalls die Überführung des Produkts in ein Salz.

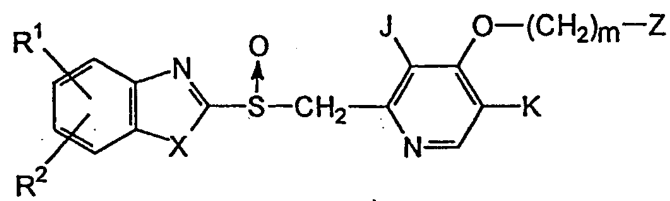
11. Verfahren nach Anspruch 10, dadurch gekennzeichnet, daß das Oxidationsmittel ausgewählt ist aus Wasserstoffperoxid, Peressigsäure, m-Chlorperbenzoesäure, Natriumhypochlorit oder Natrium-m-perjodat.

12. Verfahren zur Herstellung einer Verbindung der Formel I''':



(I''')

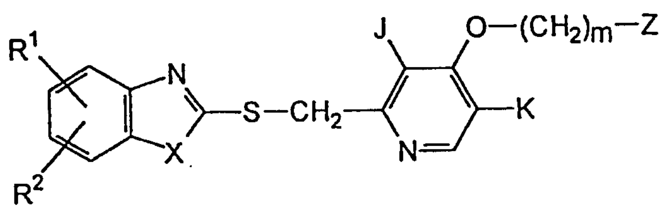
worin R^1, R^2, X, J, K, Z und m die im Anspruch 1 angegebene Bedeutung besitzen, oder einem pharmazeutisch annehmbaren Salz davon,
umfassend die Stufe der Umsetzung eines Oxidationsmittels mit einer Verbindung der Formel I'':



(I'')

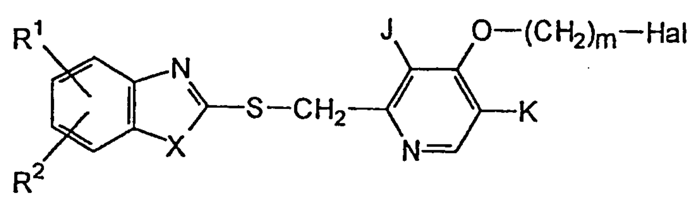
worin R^1, R^2, X, J, K, Z und m die vorstehend angegebene Bedeutung besitzen, und gegebenenfalls die Überführung des Produkts in ein Salz.

13. Verfahren zur Herstellung einer Verbindung der Formel I':



(I')

worin R^1, R^2, X, J, K, Z und m die in Anspruch 1 angegebene Bedeutung besitzen, oder einem pharmazeutisch annehmbaren Salz davon,
umfassend die Stufe der Umsetzung einer Verbindung der Formel IV:

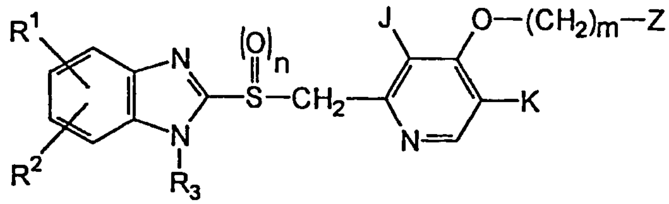


(IV)

worin R^1, R^2, X, K, J und m die vorstehend angegebene Bedeutung besitzen und Hal ein Halogenatom bedeutet, mit einer Verbindung der Formel Z-H, worin Z die vorstehend angegebene Bedeutung besitzt, und gegebenenfalls die Überführung des Produkts in ein Salz.

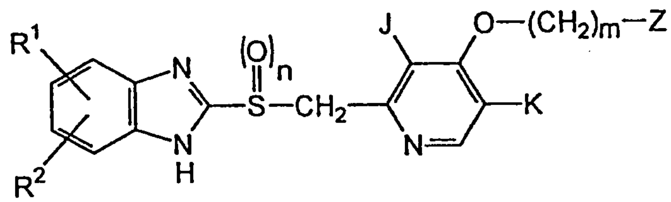
14. Verfahren nach Anspruch 13, dadurch gekennzeichnet, daß die Umsetzung in Gegenwart eines Säure-abfangenden Mittels durchgeführt wird.

15. Verfahren zur Herstellung einer Verbindung der Formel I'''':



(I'''')

worin R^1, R^2, J, K, m und Z die im Anspruch 1 angegebene Bedeutung besitzen und R^3 C_1-C_6-Alkyl, Phenyl, Benzyl oder (C_1-C_6-Alkoxy)carbonyl bedeutet, n eine ganze Zahl von 0 bis 2 ist, oder einem pharmazeutisch annehmbaren Salz davon,
umfassend die Stufe der Umsetzung der Verbindung der Formel VI



(VI)

worin R^1, R^2, n, J, K, m und Z die vorstehend angegebene Bedeutung besitzen, mit R^3Hal, worin Hal ein Halogenatom bedeutet und gegebenenfalls die Überführung des Produkts in ein Salz.

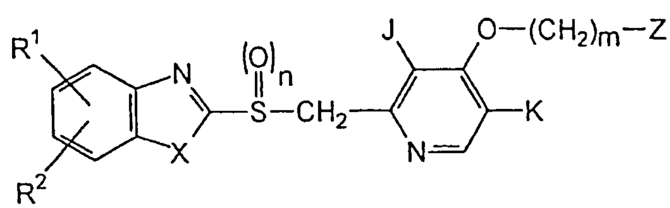
16. Verfahren nach Anspruch 15, dadurch gekennzeichnet, daß es in Gegenwart eines Dehydrohalogenierungsmittels durchgeführt wird.

17. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung zur Behandlung oder Vorbeugung von Magengeschwüren, dadurch gekennzeichnet, daß man pro Dosierungseinheit 0,1 bis 100 g des Pyridinderivats oder eines pharmakologisch annehmbaren Salzes davon, erhalten nach einem Verfahren gemäß einem der vorhergehenden Ansprüche, zusammen mit einem pharmakologisch annehmbare Träger zu einer pharmazeutischen Zusammensetzung formuliert.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Dérivé de pyridine représenté par la formule générale (I) :



(I)

dans laquelle R^1 et R^2 peuvent être identiques ou différents l'un de l'autre et chacun représente un atome d'hydrogène, un groupe alkyle en C_1-C_6, alcoxy en C_1-C_6, alkyle en C_1-C_6 halogéné, alcoxy(en C_1-C_6)carbonyle ou carboxyle ou un atome d'halogène;
X représente un groupe représenté par la formule: -O-, -S- ou

$$\begin{array}{c} -N- \\ | \\ R^3 \end{array}$$

(dans laquelle R^3 représente un atome d'hydrogène ou un groupe alkyle en C_1-C_6, phényle, benzyle ou alcoxy (en C_1-C_6)carbonyle);

Z représente un groupe représenté par la formule générale:

$$-O-(CH_2)_q-R^5$$

dans laquelle q représente un nombre entier de 1 a 3 et R^5 représente un groupe naphtyle, qui peut être substitué avec un groupe alcoxy en C_1-C_6, un groupe hydroxyle ou un atome d'halogène; un groupe pyridyle ou un groupe furyle,

n représente un nombre entier de 0 à 2; m représente un nombre entier de 2 à 10; et

J et K peuvent être identiques ou différents l'un de l'autre et chacun représente un atome d'hydrogène ou un groupe alkyle en C_1-C_6,

et un sel pharmaceutiquement acceptable de celui-ci.

2. Composé selon la revendication 1, dans lequel R^5 représente un groupe pyridyle ou un groupe furyle.

3. Composé selon la revendication 2, dans lequel R^5 représente un groupe pyridyle.

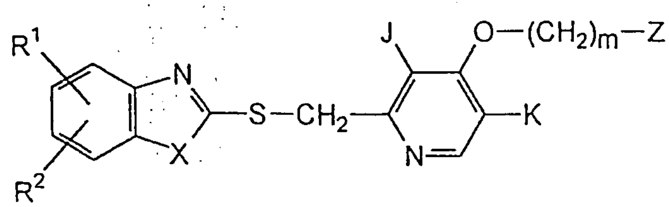
4. Composition pharmaceutique qui comprend une quantité pharmacologiquement efficace d'un dérivé de pyridine selon l'une quelconque des revendications 1 à 3 ou d'un sel pharmacologiquement acceptable de celui-ci et un support pharmacologiquement acceptable.

5. Composition pharmaceutique selon la revendication 4 qui comprend 0,1 à 100 g du dérivé de pyridine ou d'un sel pharmacologiquement acceptable de celui-ci par dose unitaire.

6. Composition pharmaceutique selon la revendication 4 ou 5 pour le traitement ou la prévention des ulcères peptiques.

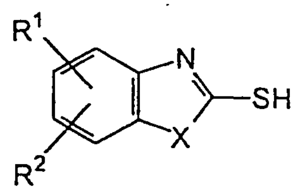
7. Utilisation d'un dérivé de pyridine selon l'une quelconque des revendications 1 à 3 pour la fabrication d'un médicament pour le traitement ou la prévention des ulcères peptiques.

8. Procédé pour la préparation d'un composé de formule générale I':



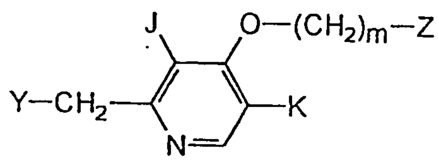
(I')

dans laquelle R^1, R^2, X, J, K, Z et m sont tels que définis dans la revendication 1,
ou d'un sel pharmaceutiquement acceptable de celui-ci, comprenant l'étape consistant à faire réagir le composé de formule II avec le composé de formule III



(II)

où R^1, R^2 et X sont tels que définis ci-dessus



(III)

où m, Z, J et K sont tels que définis ci-dessus et Y représente un atome d'halogène ou un groupe sulfonyloxy, et éventuellement la transformation du produit en un sel.

9. Procédé selon la revendication 8, dans lequel Y représente un chlore, un brome ou un iode.

10. Procédé selon la revendication 8, dans lequel Y représente un groupe alkylsulfonyloxy.

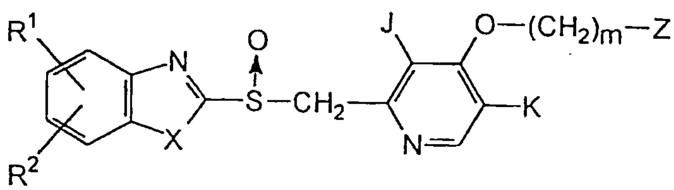
11. Procédé selon la revendication 10, dans lequel le groupe alkylsulfonyloxy est un groupe méthylsulfonyloxy ou un groupe éthylsulfonyloxy.

12. Procédé selon la revendication 10, dans lequel le groupe sulfonyloxy est un groupe sulfonyloxy aromatique.

13. Procédé selon la revendication 12, dans lequel le groupe sulfonyloxy aromatique est un benzènesulfonyloxy ou un groupe tosyloxy.

14. Procédé selon l'une quelconque des revendications 8 à 13, dans lequel la réaction est effectuée en présence d'un agent de neutralisation d'acide.

15. Procédé pour la préparation d'un composé de formule I'':

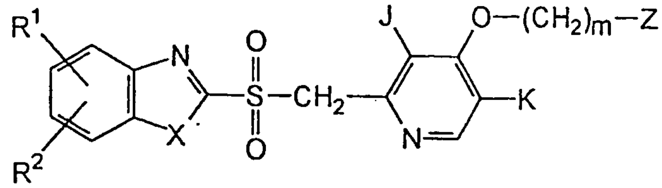


(I'')

dans laquelle R^1, R^2, X, J, K, Z et m sont tels que définis dans la revendication 1,
ou d'un sel pharmaceutiquement acceptable de celui-ci, comprenant l'étape consistant à faire réagir le composé de formule I' tel que défini dans la revendication 8 avec une quantité approximativement équimolaire d'un agent oxydant, et éventuellement la transformation du produit en un sel.

16. Procédé selon la revendication 15, dans lequel l'agent oxydant est choisi parmi le peroxyde d'hydrogène, l'acide peracétique, l'acide m-chloroperbenzoïque, l'hypochlorite de sodium ou l'hypobromite de sodium.

17. Procédé pour la préparation d'un composé de formule I''':

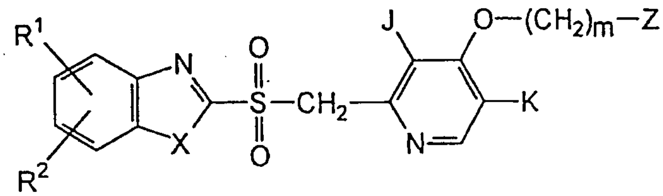


(I''')

dans laquelle R^1, R^2, X, J, K, Z et m sont tels que définis dans la revendication 1, ou d'un sel pharmaceutiquement acceptable de celui-ci, comprenant l'étape consistant à faire réagir le composé de formule I' tel que défini dans la revendication 8 avec au moins deux équivalents molaires d'un agent oxydant, et éventuellement la transformation du produit en un sel.

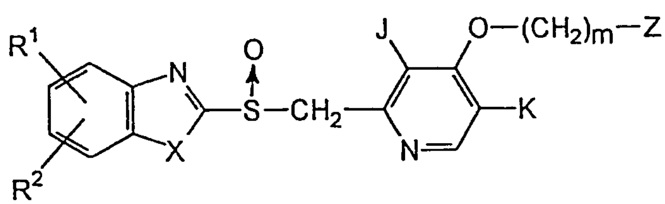
18. Procédé selon la revendication 17, dans laquelle l'agent oxydant est choisi parmi le peroxyde d'hydrogène, l'acide peracétique, l'acide m-chloroperbenzoïque, l'hypochlorite de sodium ou le m-periodate de sodium.

19. Procédé pour la préparation du composé de formule I''':



(I''')

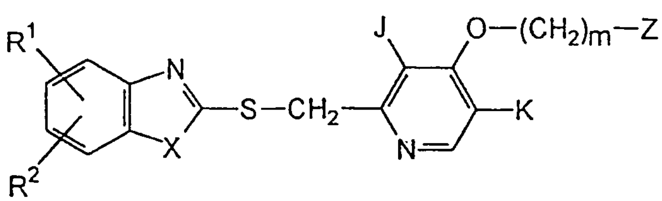
dans laquelle R^1, R^2, X, J, K, Z et m sont tels que définis dans la revendication 1, ou d'un sel pharmaceutiquement acceptable de celui-ci, comprenant l'étape consistant à faire réagir un agent oxydant avec un composé de formule I'':



(I'')

dans laquelle R^1, R^2, X, J, K, Z et m sont tels que définis ci-dessus, et éventuellement la transformation du produit en un sel.

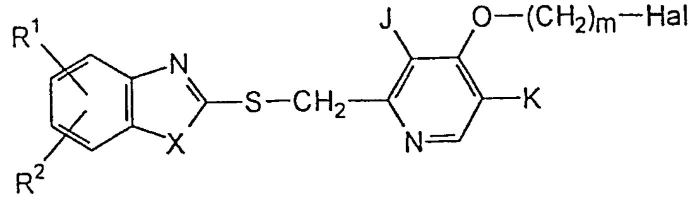
20. Procédé pour la préparation d'un composé de formule I':



(I')

dans laquelle R^1, R^2, X, J, K, Z et m sont tels que définis dans la revendication 1, ou d'un sel pharmaceutiquement acceptable de celui-ci,

comprenant l'étape consistant à faire réagir un composé de formule IV:

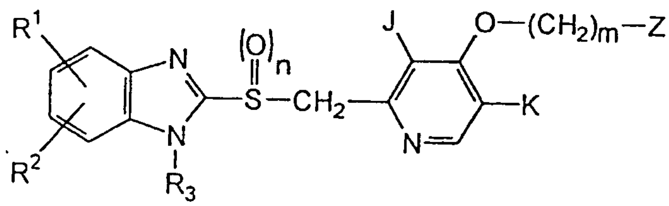


(IV)

dans laquelle R^1, R^2, X, K, J et m sont tels que définis ci-dessus et Hal représente un atome d'halogène, avec un composé de formule Z-H, dans laquelle Z est tel que défini ci-dessus, et éventuellement la transformation du produit en un sel.

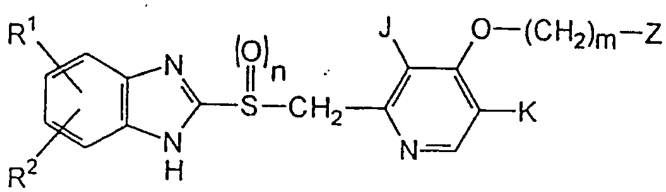
21. Procédé selon la revendication 20, dans lequel la réaction est effectuée en présence d'un agent de neutralisation d'acide.

22. Procédé pour la préparation d'un composé de formule I'''':



(I'''')

dans laquelle R^1, R^2, n, J, K, m et Z sont tels que définis dans la revendication 1 et R^3 représente un groupe alkyle en C_1-C_6, phényle, benzyle ou alcoxy (en C_1-C_6) carbonyle, ou d'un sel pharmaceutiquement acceptable de celui-ci, comprenant l'étape consistant à faire réagir le composé de formule VI:



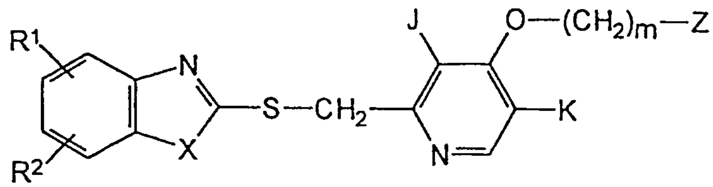
(VI)

dans laquelle R^1, R^2, n, J, K, m et Z sont tels que définis ci-dessus, avec R^3-Hal, où Hal représente un atome d'halogène, et éventuellement la transformation du produit en un sel.

23. Procédé selon la revendication 22, qui est effectué en présence d'un agent de déshydrohalogénation.

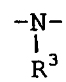
Revendications pour les Etats contractants suivants : ES, GR

1. Procédé pour la préparation d'un dérivé de pyridine représenté par la formule générale I':



(I')

dans laquelle R^1 et R^2 peuvent être identiques ou différents l'un de l'autre et chacun représente un atome d'hydrogène, un groupe alkyle en C_1-C_6, alcoxy en C_1-C_6, alkyle en C_1-C_6 halogéné, alcoxy(en C_1-C_6)carbonyle ou carboxyle ou un atome d'halogène;
X représente un groupe représenté par la formule: -O-, -S- ou



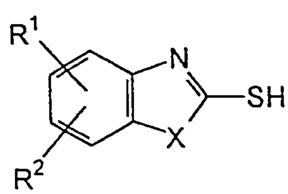
(dans laquelle R^3 représente un atome d'hydrogène ou un groupe alkyle en C_1-C_6, phényle, benzyle ou alcoxy(en C_1-C_6)carbonyle);

Z représente un groupe représenté par la formule générale:

$$-O-(CH_2)_q-R^5$$

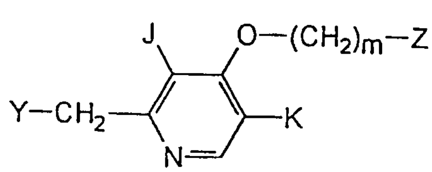
dans laquelle q représente un nombre entier de 1 à 3 et R^5 représente un groupe naphtyle, qui peut être substitué avec un groupe alcoxy en C_1-C_6, un groupe hydroxyle ou un atome d'halogène; un groupe pyridyle ou un groupe furyle,
m représente un nombre entier de 2 à 10; et
J et K peuvent être identiques ou différents l'un de l'autre et chacun représente un atome d'hydrogène ou un groupe alkyle en C_1-C_6,
et d'un sel pharmaceutiquement acceptable de celui-ci,

comprenant l'étape consistant à faire réagir le composé de formule II avec le composé de formule III



(II)

où R^1, R^2 et X sont tels que définis ci-dessus



(III)

où m, Z, J et K sont tels que définis ci-dessus et Y représente un atome d'halogène ou un groupe sulfonyloxy, et

éventuellement la transformation du produit en un sel.

2. Procédé selon la revendication 1, dans lequel Y représente un chlore, un brome ou un iode.

3. Procédé selon la revendication 1, dans lequel Y représente un groupe alkylsulfonyloxy.

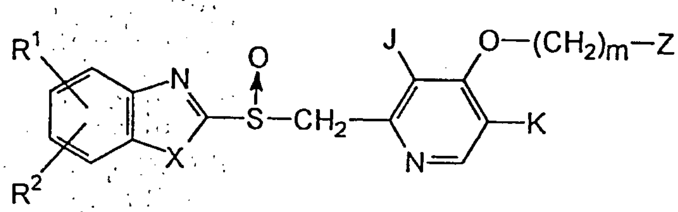
4. Procédé selon la revendication 3, dans lequel le groupe alkylsulfonyloxy est un groupe méthylsulfonyloxy ou un groupe éthylsulfonyloxy.

5. Procédé selon la revendication 3, dans lequel le groupe sulfonyloxy est un groupe sulfonyloxy aromatique.

6. Procédé selon la revendication 5, dans lequel le groupe sulfonyloxy aromatique est un groupe benzènesulfonyloxy ou un groupe tosyloxy.

7. Procédé selon l'une quelconque des revendications 1 à 6, dans lequel la réaction est effectuée en présence d'un agent de neutralisation d'acide.

8. Procédé pour la préparation d'un composé de formule I'':

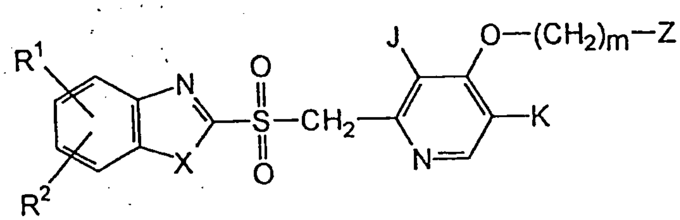


(I'')

dans laquelle R^1, R^2, X, J, K, Z et m sont tels que définis dans la revendication 1, ou d'un sel pharmaceutiquement acceptable de celui-ci, comprenant l'étape consistant à faire réagir le composé de formule I' tel que défini dans la revendication 1 avec une quantité approximativement équimolaire d'un agent oxydant, et éventuellement la transformation du produit en un sel.

9. Procédé selon la revendication 8, dans lequel l'agent oxydant est choisi parmi le peroxyde d'hydrogène, l'acide peracétique, l'acide m-chloroperbenzoïque, l'hypochlorite de sodium ou l'hypobromite de sodium.

10. Procédé pour la préparation d'un composé de formule I''':

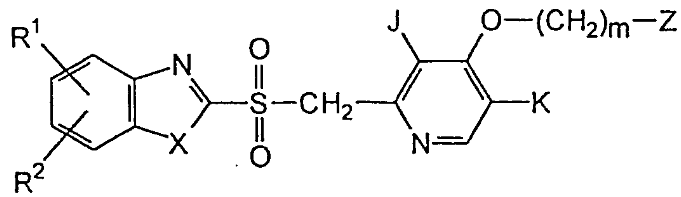


(I''')

dans laquelle R^1, R^2, X, J, K, Z et m sont tels que définis dans la revendication 1, ou d'un sel pharmaceutiquement acceptable de celui-ci, comprenant l'étape consistant à faire réagir le composé de formule I' tel que défini dans la revendication 1 avec au moins deux équivalents molaires d'un agent oxydant, et éventuellement la transformation du produit en un sel.

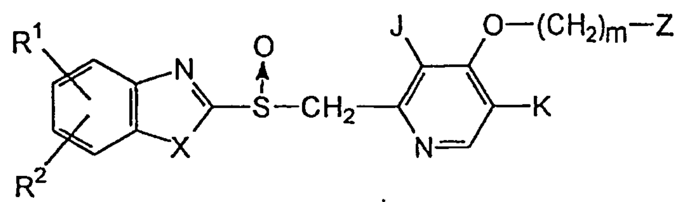
11. Procédé selon la revendication 10, dans lequel l'agent oxydant est choisi parmi le peroxyde d'hydrogène, l'acide peracétique, l'acide m-chloroperbenzoïque, l'hypochlorite de sodium ou le m-periodate de sodium.

12. Procédé pour la préparation du composé de formule I'''':



(I''')

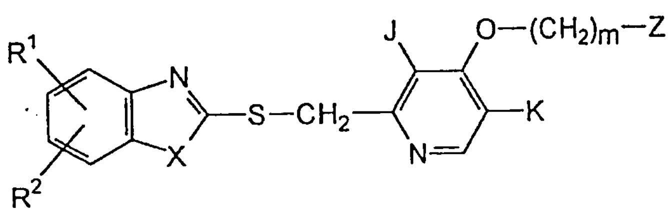
dans laquelle R^1, R^2, X, J, K, Z et m sont tels que définis dans la revendication 1, ou d'un sel pharmaceutiquement acceptable de celui-ci, comprenant l'étape consistant à faire réagir un agent oxydant avec un composé de formule I":



(I")

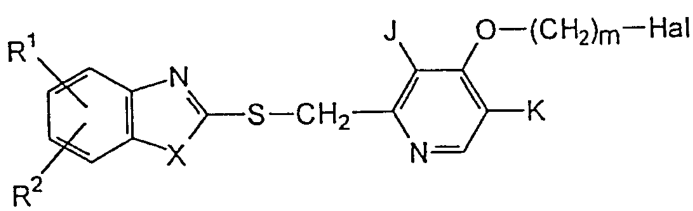
dans laquelle R^1, R^2, X, J, K, Z et m sont tels que définis ci-dessus, et éventuellement la transformation du produit en un sel.

13. Procédé pour la préparation d'un composé de formule I':



(I')

dans laquelle R^1, R^2, X, J, K, Z et m sont tels que définis dans la revendication 1, ou d'un sel pharmaceutiquement acceptable de celui-ci,
comprenant l'étape consistant à faire réagir un composé de formule IV:

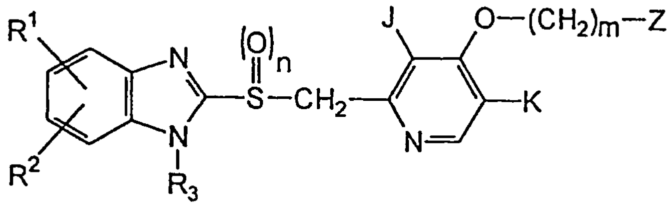


(IV)

dans laquelle R^1, R^2, X, K, J et m sont tels que définis ci-dessus et Hal représente un atome d'halogène, avec un compose de formule Z-H, dans laquelle Z est tel que défini ci-dessus, et éventuellement la transformation du produit en un sel.

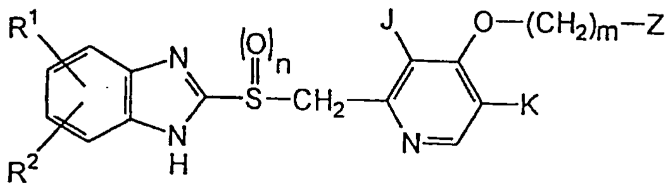
14. Procédé selon la revendication 13, dans lequel la réaction est effectuée en présence d'un agent de neutralisation d'acide.

15. Procédé pour la préparation d'un composé de formule I'''':



(I'''')

dans laquelle R^1, R^2, J, K, m et Z sont tels que définis dans la revendication 1 et R^3 représente un groupe alkyle en C_1-C_6, phényle, benzyle ou alcoxy(en C_1-C_6)carbonyle, n représente un nombre entier de 0 à 2, ou d'un sel pharmaceutiquement acceptable de celui-ci, comprenant l'étape consistant à faire réagir le composé de formule VI:



(VI)

dans laquelle R^1, R^2, n, J, K, m et Z sont tels que définis ci-dessus, avec R^3-Hal, où Hal représente un atome d'halogène, et éventuellement la transformation du produit en un sel.

16. Procédé selon la revendication 15, qui est effectué en présence d'un agent de déshydrohalogénation.

17. Procédé de préparation d'une composition pharmaceutique pour le traitement ou la prévention des ulcères peptiques qui comprend la formulation de 0,1 à 100 g du dérivé de pyridine ou d'un sel pharmacologiquement acceptable de celui-ci par dose unitaire obtenu par un procédé selon l'une quelconque des revendications précédentes avec un support pharmacologiquement acceptable.